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Does the COVID-19 Pandemic Have an Impact on Compassion Fatigue among Midwives?

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ABSTRACT

Professional health services have been key in the recovery of patients during the COVID-19 pandemic. Health professionals have been in a great effort to meet the care needs of patients despite experiencing a high emotional burden for reasons such as unknown treatment of the disease, high contagiousness, changing working systems, increased workload, and the need to wear protective equipment. The unknown effects of the virus on the health of mothers and babies increased the concerns of midwives helping families in the core of society, which are the most intimate areas, regarding the risk of infection. Midwives had to manage an exhausting process similar to the one experienced by nurses, when they continued providing secondary health services such as immunization, antenatal care, and follow-ups. They are among the health professionals forced to work under highly adverse conditions, such as increased duties and responsibilities in the pandemic, and cancellation of leaves. It is reported that midwives, who are forced to work outside their field of duty due to the pandemic, are highly likely to experience compassion fatigue and to have a low level of life quality as well as professional belonging. Qualitative studies conducted with midwives working in the delivery room reported that midwives in delivery rooms experience compassion fatigue, adopt the concept of compassion fatigue, come up with their own solutions or receive psychological support to deal with compassion fatigue, and that they suggested that psychological support needs be provided by the state. As a result, many mothers and pregnant women lost their lives in this ongoing pandemic process , many health professionals lost their lives due to the epidemic. Midwives are one of these health professionals. The feeling of helplessness at the beginning of the pandemic, the unknowns about its treatment made the working conditions even more difficult. Considering these, it is reasonable to argue that midwives have been likely to experience compassion fatigue.

Keywords: Compassion Fatigue, Midwifery, COVID-19

COVID-19 Pandemisinin Ebelerde Merhamet Yorgunluğuna Etkisi var mı?

Süreç

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ÖZ

Covid-19 pandemisinde hastaların iyileşme sürecinde profesyonel sağlık hizmetlerinin çok önemli bir yeri bulunmaktadır. Bu süreçte sağlık profesyonelleri hastalığın tedavisinin bilinmemesi, bulaş riskinin fazla olması, çalışma sistemlerinin değişmesi, iş yüklerinin artması, koruyucu ekipman ile çalışmak zorunda kalmaları gibi nedenlerle yüksek duygu yükü yaşamalarına rağmen hastaların bakım gereksinimlerini karşılamaya çalışmaktadırlar. Ebelik mesleğinde de pandeminin anne bebek sağlığı üzerindeki etkilerinin bilinmezliği, en mahram alanlar olan toplumun çekirdeğinde yer alan aileler ile çalışan ebelerin bulaş riskine karşın endişelerini arttırmıştır. Ebeler bağışıklama, antenatal bakım gereksinimleri, izlemler, ikinci basamak sağlık hizmetlerini sürdürmeye devam ettikleri pandemi sürecinde hemşireler ile benzer olarak yıpratıcı bir süreci yönetmek zorunda kalmışlardır. Pandemi sürecinde artan görev ve sorumluluklar, izinlerin iptal edilmesi gibi pek çok olumsuz şartlar altında çalışmaya mecbur kalan sağlık grubu arasında yer almaktadır. Pandemi ile görev alanı dışında çalışmaya maruz kalan ebelerin merhamet yorgunluğu yaşama düzeyi yüksek olduğu saptanırken, yaşam kalite düzeylerinin düşük olduğu aynı zamanda mesleki aidiyetlerinin de düşük olduğu saptanmıştır. Doğumhanede çalışan ebeler ile yapılan nitel çalışmalarında doğumhanede çalışan ebelerin merhamet yorgunluğu yaşadıkları, merhamet kavramını benimsedikleri, merhamet yorgunluğu ile baş etmek için kendi çözüm yöntemlerini bularak ya da profesyonel psikolojik destek aldıklarını belirterek, psikolojik destek gereksinimlerinin devlet tarafından sağlanması önerisinde bulunmuşlardır. Sonuç olarak devam eden pandemi sürecinde birçok anne ve gebe ile pandemi kaynaklı birçok sağlık profesyoneli hayatını kaybetmiştir. Ebelerde pandemi döneminde hayatını kaybeden meslek grubunda yer almıştır. Pandeminin başladığı ilk anlardaki çaresizlik hissi, tedavisi hakkındaki bilinmezlikler çalışma koşullarını daha da zorlaştırdığı düşünülmektedir. Tüm bu durumlar göz önünde bulundurulduğunda ebelerin merhamet yorgunluğu yaşamalarının olası olduğu kanısına varılmıştır.

Anahtar sözcükler: Merhamet Yorgunluğu, Ebelik, Covid19

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Introduction

Covid-19 Pandemic

Coronaviruses that cause mild respiratory infections were first described in 1960 [1]. These pathogens, which have various types, are RNA viruses, the types of which infect animals and humans are different from each other [2]. COVID-19 is an epidemic caused by the SARS-CoV-2 virus that affects the whole world. After the first cases were reported in the city of Wuhan, province of Hubei, China, on December 31, 2019, it has rapidly spread all over the world. The cases rapidly increased among animals and humans, affecting 30 countries negatively, as well as infecting 15,538,736 people, including health professionals, and causing a global crisis that caused the death of 634,325 people [4] The first coronavirus case in Turkey was reported on March 11, 2020 [3]. Again in Turkey, the number of confirmed COVID-19 cases was recorded as 223,315, and the number of deaths was reported as 5,563 [4]. Complications related to COVID-19 may be mild as upper respiratory tract infection or more severe, including various systemic and pulmonary symptoms [5]. Although not all of the symptoms associated with COVID-19 are permanent, some are reported to be so [6].

Those infected with COVID-19 are vulnerable to or have a weakened immune system to other respiratory infections. The declaration of the COVID-19 as an epidemic by the World Health Organization also negatively affected the health of the mother and child. Coronavirus affects individuals of all ages and genders; pregnant women, those with chronic diseases, and those with immunodeficiency or low immunity are at an increased risk. Due to some physical and hormonal factors, during pregnancy, women have a higher risk of suffering from respiratory tract infections [9,10].

During pregnancy, hypoxia occurs through suppression of immunity, dryness of nasal mucosa due to increased progesterone levels, and the pressure of the enlarged uterus on the diaphragm 9. The COVID-19 pandemic negatively affects the physiology and immune response of pregnant women, posing a serious threat to the well-being of the fetus and mother, which can lead to conditions requiring hospitalization or follow-up [11].

The meta-analysis study of Capobianco et al. [16], which reviews the articles published from December, 2019 to April 15, 2020, reported that pregnant women were admitted to the hospital with cough and fever, that maternal complications and cesarean delivery constituted 45% of all cases, and that approximately 20% of the pregnant women were transferred to the intensive care unit. While the frequency of preterm births is 23%, the most common neonatal complication is pneumonia and respiratory distress syndrome. It should be noted that pregnancy is an emotional process as well as a physical one.

At the beginning of the COVID-19 epidemic, there were many unknowns about its treatment, but it was known that it causes social stigma, isolation, depression and fear of death, high contagiousness, high mortality, and morbidity [12]. The symptoms the virus caused and might have were not known for certain, and the number of fatalities and ICU admissions affected individuals physiologically, socially, and psychologically.

The COVID-19 pandemic process entailed some changes in human relations and adaptation. Due to the outbreak, curfews were imposed, and visits by relatives to see a newborn, patient visits, condolence visits, and weddings were postponed [17]. The measures taken to control the epidemic and prevent its spread negatively affected education and social life. The workload and capacities of health institutions and organizations were maximized. Glasses, face masks, and one-piece suits were used to combat the pandemic. In this process, midwifery, which is a profession of empathy, underwent an emotionally challenging process even though it is one of the professions where the feelings of touch, compassion, and mercy are most intense in one-to-one contact with women. Research on the psychological effects of the pandemic on health workers is available in the literature. During the pandemic, health professionals who are active in health care services suffered from sleep deprivation as well as secondary trauma and stress disorder [37]. Research performed with nurses during the COVID-19 reveal that the most common psychological problems among them are anxiety, burnout, depression, sleep problems, and secondary trauma stress reactions [19, 22, 23, 24, 25]. Nurses and midwives, who are closely interested in patients' needs during this epidemic and under stress and intensive workload, were affected equally by the epidemic [20,21]. Health professionals also experienced an exhausting process during the management of the pandemic. Although Coronavirus, in particular, is an RNA virus that requires droplet and contact isolation, the risk of being infected with this virus is very high among midwives and nurses employed in these areas, especially in the maternity ward, intensive care, operating rooms, and emergency services [7, 8].

The Effect of The Pandemic On Compassion Fatigue In Midwives

The provision of care and support by primary and secondary health institutions during the pandemic reduced the quality and efficiency of midwifery services [13]. Midwives and nurses, who had a key role in the international health system since the start of the pandemic, went through a difficult process to provide quality care at every stage of the fight against the epidemic [14]. Midwives and nurses are already responsible for care planning, implementing high-capacity strategies, and triage in emergency departments and secondary and tertiary health centers, scanning the people in the testing centers, educating the public, and providing information on infection control methods to staff, protecting public health, promoting the use of personal protective equipment, protecting immunocompromised patients, and providing care to all patients with a compassionate and empathetic approach; through the COVID-19 pandemic, the number of patients requiring their care increased [14, 15].

The midwives working in the field were employed in their own fields of work before the pandemic; however, they are employed in the fields where they assumed the caring and protective roles of the midwifery profession, especially in the emergency department, intensive care units, pandemic services, following the pandemic. In their cross-sectional descriptive study, Yakut et al., [18] noted that the increased workload and perceived lack of social support caused occupational burnout among health workers during the pandemic.

The pre-pandemic studies on compassion fatigue among midwives showed that midwives also defined the concept of compassion as empathy and experienced compassion fatigue before the pandemic, but did not receive social and financial support from the institution where they work [29, 30, 31] As the pandemic represented the state of emergency in health, midwives continued to work in many areas other than their fields (including contact tracing teams, intensive care, emergency, pandemic services), which is directly related to the concepts of professional belonging, job satisfaction, burnout and causes compassion fatigue [32, 36]. After the World Health Organization declared 2020 as the "year of the nurse and midwife", the coronavirus, which affected the whole world in a short time, made the working conditions of midwives even more difficult; it is believed that this may increase anxiety and fear, and cause occupational burnout [33, 38]. There was no interruption in midwifery care and counseling services during the COVID-19 pandemic. In wars, peace, famines, and disasters, women and children need qualified midwifery care.

In this regard, this study focuses on the importance of the concept of compassion fatigue based on the implications of the COVID-19 pandemic and its possible effects on midwives and presents possible solutions. The role and place of midwives in society cannot be underestimated or denied. The International Midwifery Confederation (ICM) underlined that midwives should be proud of their extraordinary effort and work during the pandemic [34]. Online studies were carried out in a number of areas during the pandemic. One of these areas is midwifery care and services. Education and counseling services were not interrupted due to the pandemic, and support was provided through phone calls and social networks instead of physical environments [35]. These practices were very efficient for the continued provision of care. However, the increased workload seems to have a negative impact on midwives.

Compassion Fatigue

The first definition of compassion fatigue was proposed by Joinson, who studied burnout among nurses working in the emergency department [26]. Despite not proposing a complete definition, Joinson stated that nurses providing empathetic care might internalize the traumas and pain of the patients they care for and provide services for, and explained the concept of compassion fatigue as *"a unique form of burnout that affects caregivers"*. In different research, Joinson's definition of compassion fatigue is defined as one's experiencing burnout or the cost of care, although s/he does not have any frustration with the system or problem affecting job satisfaction [27, 28].

With the COVID-19 pandemic, working conditions in the field of health, which entails multidisciplinary work, have become even more strict. The rapid spread of the disease, high mortality and morbidity rates, increased need for afterlife care and support, changes in operations and equipment, low level of social support expected as a result of time spent away from the family and social environment, exposure to stigmatization, witnessing infection and/or death of colleagues, adversely affected midwives and increased their likelihood of experiencing compassion fatigue.

Being at the center of the family and therefore the society during the pandemic, midwives did not avoid taking on duties and responsibilities and were in the frontline from the beginning to the end of the pandemic, are inevitably among the occupational groups most affected by the negative effects of the

pandemic. Still, some changes in the working conditions of midwives may decrease their occupational burnout, increase their quality of life, prevent any secondary trauma and stress disorder, enhance their sleep quality, and minimize the compassion fatigue experienced by them. It is expected that increasing the number of midwives actively working during and after the pandemic, reducing the weekly working hours, and positive regulations on personnel rights and wages would boost midwives' job satisfaction and satisfaction levels. In-service training and motivation meetings would also be helpful. Moreover, the literature review yields that there are not enough studies on compassion fatigue among midwives. Further studies on midwives would have a contribution to the field.

Conclusion and Suggestions

Midwives, who have been involved in every stage of the pandemic from the very beginning, may experience compassion fatigue because of occupational burnout, decreased quality of life, increased responsibility, and workload. Institutional and/or psychological support should be offered to midwives, and such support should be affordable. There are limited studies on the levels of compassion fatigue experienced by midwives in the field of midwifery. Future studies that investigate the fatigue of midwives in national and international literature would contribute to the field.

References

1. Mcintosh, K., Samp; Perlman, S. (2015). Coronaviruses, Including Severe Acute Respiratory Syndrome (SARS) And Middle East Respiratory Syndrome (MERS). Mandell, Douglas, And Bennett’s Principles And Practice Of Infectious Diseases, 1928.
2. Ak, Ö. (2020). Soğuk Algınlığından Ölümcül Kabusa. Küresel Salgın. Https://Tubitak.Gov.Tr/Sites/Default/Files/18842/Bilim_Ve_Teknik_Coronavirus_Hakkinda.Pdf
3. T.C. Sağlık Bakanlığı, Halk Sağlığı Genel Müdürlüğü. Covid-19 Rehber. Ankara:T.C. Sağlık Bakanlığı; 2020. Available From: Https:// Covid19.Saglik.Gov.Tr/Tr-66301/Covid-19-Rehberi.Html
4. World Health Organization,(2019).Who Coronavirus Disease (Covid-19) Dashboard. Available From: Https://Covid19.Who.Int/ (Et.11.11.2022)
5. Hapshy V, Aziz D, Kahar P, Khanna D, Johnson Ke, Parmar Ms (2021) Covid-19 And Pregnancy: Risk, Symptoms, Diagnosis, And Treatment. Sn Compr. Clin. Med. 3: 1477–148
6. Carfì A, Bernabei R, Landi F (2020) Persistent Symptoms In Patients After Acute Covid-19. Jama 324(6):603-605.
7. İzmir Tabip Odası.2019 İzmir’de Covid-19 Tanılı Sağlık Çalışanları. Available From: Http://Www.Izmirtabip.Net/Uncategorized/Izmirde-Covid-19- Tanili-Saglik-Calisanlari/(E.T 11.11.2022).
8. Boelig Rc, Manuck T, Oliver Ea, Di Mascio D, Saccon G, Bellussi F, Et Al,2020. Labor And Delivery Guidance For Covid-19. Am J Obstet Gynecol Mfm.2020;2(2):100110. Doi: 10.1016/J.Ajogmf.2020.100110.
9. Daniel, P., Hills, T., &Amp; Lim, W. S. (2020). Pulmonary Infections In Pregnancy. Respiratory Disease In Pregnancy, 57.
10. Mathad, J. S., Samp; Gupta, A. (2017). Pulmonary Infections In Pregnancy. Seminars In Respiratory And Critical Care Medicine, 38(02), 174–184.
11. Liu H, Wang Ll, Zhao Sj, Kwak-Kim J, Mor G, Liao Ai (2020). Why Are Pregnant Women Susceptible To Covid-19? An Immunological Viewpoint. J Reprod Immunol 139: 103-122
12. Yılmaz, Y., Erdoğan, A., &Amp; Hocaoğlu, Ç. (2021). Covid-19 Ve Damgalanma. Kocaeli Tıp Dergisi, 10(Supp: 1), 47-55.
13. Özkan, S., Yildirim, D. F., &Amp; Sercekus, P. (2022). Covid-19 Pandemisinin Gebelerin Ruh Sağlığı Üzerindeki Etkisi Ve Hemşirenin Rolü. Ordu Üniversitesi Hemşirelik Çalışmaları Dergisi, 5(2), 269-273.
14. Dalglısh Sl. (2020). Covid-19 Gives The Lie To Global Health Expertise, The Lancet, 395,10231: 1189.

15. Green J, Doyle C, Hayes S. (2020). Newnham W, Et Al, Covid-19 And District And Community Nursing, British Journal Of Community Nursing, 25(5):213.

16. Capobianco G, Saderi L, Aliberti S, Mondoni M, Piana A, Dessole F, Dessole M, Cherchi Pc, Dessole S, Sotgiu G (2020).Covid-19 In Pregnant Women: A Systematic Review And Meta-Analysis. Ejog 252: 543- 558

17. Bitusikova, A., Covid-19 And Funeral-Byzoom. Edited By Giuliana B. Prato,(2020). Https://Www.Gov.Scot/Publications/Coronavirus

18. Yakut, E., Özlem, Kuru Ve Güngör, Y. (2020). Sağlik Personelinin Covid-19 Korkusu İle Tükenmişliği Arasindaki İlişkide Aşiri İş Yükü Ve Algilanan Sosyal Desteğin Etkisinin Yapisal Eşitlik Modeliyle Belirlenmesi. Ekev Akademi Dergisi , (83), 241-262.

19. Özalp, Ş. Ş. (2021). Covid-19 Pandemisinde Hemşirelerin Ödediği Bedel: Merhamet Yorgunluğu. Journal Of Innovative Healthcare Practices, 2(2), 80-87.

20. Billings, J., Greene, T., Kember, T., Grey, N., El-Leithy, S., Lee, D., Kennerley, H., Albert, I., Robertson, M., Brewin, C. R., &Amp; Bloomfield, M.(2020). "Supporting Hospital Staff During Covıd-19: Early Interventions". Occupational Medicine. Vol.70, No.5, Pp.327–329,2020.

21. Jackson D, Bradbury-Jones C, Baptiste D, Gelling L, Morin K, Neville S, Smith Gd, (2020)."Life In The Pandemic: Some Reflections On Nursing In The Context Of Covid-19". Journal Of Clinical Nursing, Vol.29, No:13-14, P.2041-2043. 2020.Doi.Org/10.1111/Jocn.15257

22. Çevik Aktura S, Özden G. (2020). "Salgının Psikolojik Etkileri: Covıd-19 Hemşireleri". Uluslararası Sosyal Araştırmalar Dergisi, Vol.13, No.73, 2020.

23. Hiç Durmaz D, Üzar Özçetin Ys. (2020) "Covıd-19 Pandemisinde Ön Safta Çalışan Hemşirelerin Ruhsal Sağlığının Korunması Ve Ruhsal Travmanın Önlenmesi".Huhemfad-Johufon, Vol.7(Özel Sayı), P.1- 7, 2020.

24. Lai, J., Ma, S., Wang, Y., Cai, Z., Hu, J., Wei, N., Wu, J., Du, H., Chen, T., Li, R., Tan, H., Kang, L., Yao, L., Huang, M., Wang, H., Wang, G., Liu, Z., &Amp; Hu, S. (2019). "Factors Associated With Mental Health Outcomes Among Health Care Workers Exposed To Coronavirus Disease 2019". Jama Network Open, Vol.3, No.3, 202.

25. Alharbi J, Jackson D, Usher K, (2020). "The Potential For Covid-19 To Contribute To Compassion Fatigue In Critical Care Nurses", J Clin Nurs, Vol.29, P.2762–2764, 2020.

26. Joinson C. (1992). "Coping With Compassion Fatigue" Nursing. Vol. 22, No.4, P.116-120, 1992.

27. Orlovsky C. (2006). "Compassion Fatigue",Prairie Rose. Vol.75, No.13, 2006

28. Circenis K, Millere I. (2011). "Compassion Fatigue, Burnout And Contributory Factors Among Nurses In Latvia". Procedia-Socialand Behavioral Sciences, Vol.30:Pp.2042–46. 2011

29. Sökmen, Y., &Amp; Taşpinar, A. (2021). Doğumhanede Çalişan Ebelerde Merhamet Yorgunluğu Algisi: Nitel Bir Çalişma. Samsun Sağlık Bilimleri Dergisi, 6(1), 55-62.

30. Qu L, Gao J, Liu L, Lun B, Chen D. (2022). Doğumhanede Çalışan Çinli Ebeler Arasında Merhamet Yorgunluğu Ve Merhamet Memnuniyeti: Kesitsel Bir Anket. Ebelik. 2022 Ekim; 113:103427. Doi: 10.1016/J.Midw.2022.103427. Epub 2022 9 Temmuz. Pmid: 35853335.

31. Katsantoni K, Zartaloudi A, Papageorgiou D, Drakopoulou M, Misouridou E. (2019) Prevalence Of Compassion Fatigue, Burn-Out And Compassion Satisfaction Among Maternity And Gynecology Care Providers In Greece. Mater Sociomed. 2019 Sep;31(3):172-176. Doi: 10.5455/Msm.2019.31.172-176. Pmid: 31762697; Pmcid: Pmc6853751.

32. Turan, İ. (2021). Ebelerde Mesleki Aidiyetin Merhamet Yorgunluğu Ve Yaşam Kalitesine Etkisi (İnönü Üniversitesi Sağlık Bilimleri Enstitüsü).

33. Fatma, B. A. Y., &Amp; Ataş, A. N. (2021). 2020 Uluslararası Ebelik Ve Hemşirelik Yılı: Covid-19'un Gölgesinde Ebelik Mesleği. İzmir Katip Çelebi Üniversitesi

Sağlık Bilimleri Fakültesi Dergisi, 6(1), 49-53.

34. Bick D. Covid-19:(2020). Is The International Year Of The Midwife. Midwifery. 2020;85(June 2020, 102719).

35. Renfrew Mj, Cheyne H, Craig J, Duff E, Dykes F, Hunter B, Et Al. (2020). Sustaining Quality Midwifery Care In A Pandemic And Beyond. Midwifery Internet. 2020 Sep;88(January):102759. Available From: Https:// Linkinghub.Elsevier.Com/Retrieve/Pii/S0266613820301315

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Professional Identity in Midwifery

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ABSTRACT

Professionalism is defined as "the service conducted by highly educated professionals, prepared to use their knowledge and skills in the interests of others, adhered to ethical standards, and supported by relevant professional organizations."

Professionalism affects both the individual and the society. The development of professionalism in a professional group provides quality service delivery to the community while the strengthening of professional identities for professional members.

Midwifery; women are an important professional group because of its role in child, family and community health. Thus, it is important for the maternity profession that provides the health and well-being of the community, to choose a conscious and optional career. To do this, professional informations must be made to students who will make college choices. It is necessary to organize seminars on the development of professional midwifery identity, to identify and identify factors affecting their professionalism, in which midwifery students are taught about values and ethics during the course of education and training.

In Turkey, there are factors that result in parents becoming embroiled in professional identity. The most significant cause of this confusion is due to legal regulations concerning the duties of midwives with different duties and responsibilities from nurses, but there are still ongoing complexities between the two professional groups in the workplace. The work of midwives in non-professional areas causes identity confusion and negatively affects their role as professionals. In this context, it is recommended to carry out more cross-sectional and experimental studies that will enable the development of professional identities of midwives.

Keywords: Professionalism, midwifery, professional identity

Ebelikte Profesyonel Kimlik

Süreç

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ÖZ

Profesyonellik, “alanında yüksek düzeyde eğitim almış uzman kişilerce yürütülen, bilgi ve becerilerini başkalarının çıkarları doğrultusunda kullanmaya hazır olan, etik standartlara bağlı ve ilgili meslek örgütleriyle desteklenerek sunulan hizmet” şeklinde tanımlanmaktadır. Profesyonellik hem bireyi hem toplumu etkilemektedir. Bir meslek grubunda profesyonelliğin gelişmesi, topluma kaliteli hizmet sunumu sağlarken, meslek üyelerin de ise profesyonel kimliklerinin güçlenmesine olanak tanır.

Ebelik; kadın, çocuk, aile ve toplum sağlığında rol alması nedeniyle önemli bir meslek grubudur. Bu nedenle toplumun sağlığı ve refahını sağlayan ebelik mesleği için meslek seçiminde bilinçli ve isteğe bağlı meslek tercihi önemlidir. Bunun için ise üniversite tercihi yapacak öğrencilere mesleki bilgilendirmeler yapılmalıdır. Ebelik öğrencilerinin ise eğitim-öğretim süresince değerler ve etik konusunda eğitildiği, profesyonel ebelik kimliğini gelişmesini sağlayacak toplantılar seminerler düzenlenmesi ve profesyonelliklerini etkileyen faktörlerin belirlenmesi ve bunlara yönelik girişimlerin yapılması gerekmektedir.

Türkiye’de ebelerin mesleki kimlik karmaşası yaşamasına neden olan faktörler vardır. Bu karmaşaya neden olan en önemli sebep, ebelerin hemşirelerden farklı görev ve sorumluluklarının olduğu ebelerin görevleriyle ilgili yasal düzenlemelerine karşın, çalışma alanlarında iki meslek grubu arasında halen devam eden karmaşalar bulunmaktadır. Ebelerin meslek dışı alanlarda çalışması kimlik karmaşası yaşanmasına neden olmakta ve profesyonel kimliklerini rollerini olumsuz etkilemektedir. Bu bağlamda, ebelerin mesleki kimliklerinin gelişmesini sağlayacak daha fazla kesitsel ve deneysel çalışmalar yapılması önerilmektedir.

Anahtar sözcükler: Profesyonellik, ebelik, mesleki kimlik

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Introduction

Professionalism which is valued in contemporary societies can be described as "a practice conducted by the individuals who have received higher education of their specialty, who are ready to utilize their knowledge on behalf of other people's wellbeing, who stand on their own legs, who are sticked to the moral standards, who are supported by professional associations and people who proved themselves" [1,2].

Occupational professionalism, on the other hand, is a kind of professionalism that turned into institutive professionalism rather than individual.[2]. Professionalism is an integration of an individual's characteristics with their occupational skills and knowledge.

Professional individuals are the people who try to improve society in terms of altruism; they are autonomous, researchers open to learning. They have creative and innovative ideas and unique skills. They are well-informed and sticked to moral and occupational values [3].

Professionalism is such an important concept in any kind of occupational group since it affects both individuals and society. While professionalism create conditions for establishing occupational standards and lead to offering quality services, it also plays a crucial role in improving professional identities and therefore, all employees must adopt it. Losing occupational professionalism may lead to a decrease in service quality and disruption of care, dissatisfaction of the service recipients, and job satisfaction of the service providers, along with institutional problems.

The common goal of health systems all over the world is to provide effective and qualified services to society. In order to reach to the services with preferred quality health workers must be qualified and skilled. Midwives who play an active role in prenatal, delivery and postnatal maternal and newborn care and tracing; sexual and reproductive health services for the community are such an important professional group because of their role in women, children, family, and community health. [4]. They also preserve, improve, and enhance health within public health services [4,5]. As the midwifery profession is a profession group based on knowledge and moral values, which is carried out with the master-apprentice relationship passed down from generation to generation, there have been developments made following the alterations and innovations in the field of health. In modern days, it has become a professional group which has achieved a professional identity by education.

In our country, midwifery education started with primary school, continued with health schools, high schools, and associate degree. The most important decision in midwifery education is 'The decision of the Supreme Health Council in 1995 to carry out midwifery education at bachelor's degree level in Health Colleges'. Since 1996, with the decision numbered 96/8655, bachelor's degree level education has been given in universities. Following that, post-graduate education, master's degree (2003), and doctorate program have been commenced. Now, it is aimed by YÖK that students who enter university must be equipped with specific standards in their education. These standards, which include occupational knowledge and skills, are:

• Prenatal examination and counseling of at least 100 pregnant women,
• Pregnancy examination of at least 40 pregnant women,
• Delivering at least 40 births, (In cases where the birth counts are not enough, if the student participates 20 births, this number can be downgraded to 30.)
• Active participation to breech delivery or working on a simulation,
• Application of episiotomy or working on a simulation,
• Examination of at least 40 women with potential risk factor during birth or postnatal periods.
• Examination of at least 100 puerperant and newborn children and caring,
• Caring for newborns who require special care such as premature, postmature, low birth weight,
• Caring for women with gynecological diseases,
• Participate in medical and surgery care [6].

The midwifery profession has been developing over the years with its education and academic staff [4]. In order for the occupational identities of midwives to be improved, education in bachelor's degree and post-graduate degree is significant. With increasing researches in the field, midwives nowadays became people who are self-developing, innovative, capable of leadership, responsible, and who have high communication skills. Therefore, midwives have made progress in professionalism. However, they couldn't have sufficient occupational authority[1].
In Turkey, there are factors that lead midwives to experience professional identity confusion and prevent their professionalization. The most important and primary reason for this confusion is the difficulties in defining midwifery, and despite

the legal regulations on the duties and responsibilities of midwives, which are different from those of nurses, there are still ongoing conflicts between the two professions in their working areas [7]. While nursing is defined as a professional group that takes part in the protection and improvement of the health of individuals, family, and society and which plays a role in recovery and rehabilitation processes in cases of illness; the occupational professionalization strategies of the midwifery profession were reconsidered in the 1990s. Regarding these strategies, professional midwives are defined as people who can handle crises, have problem-solving skills, are educated, can take initiatives to protect and improve public health, and independently manage newborn and women's health during pregnancy, birth, and postnatal periods. Additionally, holistic care's ethical and social justice principles are becoming increasingly important in midwives' practice. In this way, the roles of midwives have been quite extended. [8,9]. However, because of the challenges in the professionalization process of midwifery, such as being supervised by the medical profession, and because of the education based on conventional practices, midwifery has been described as a semi-professional profession [10].

The second reason is that there are not yet a sufficient number of academic midwives in universities providing midwifery undergraduate and postgraduate education and that midwifery education is generally carried out by faculty members in the field of nursing [11]. Because of the lack of academic staff in midwifery programs, education quality is poorly affected. The reason for this is the lack of staff appointments. Thirdly, there are differences in midwifery education levels [12]. Fourth, they are de-identified as "family health workers" within the health system. And finally, midwives' working in unprofessional fields causes identity confusion and negatively affects their professional identity and role [13].

Conclusion

Midwives play a key role in enhancing public health. For this reason, it is a profession that is required to be professionalized in the field of health. The basis of professionalism is professional commitment and organization [14]. And professional identity influences the choice of profession [15]. The foundations of adopting the profession and professional practices are created during the student years. Therefore, conscious and voluntary choice of profession is important for the midwifery profession, which provides the health and welfare of society [15]. In this regard, vocational information should be provided to students who will make university choices. Preferring this profession willingly lets students be more successful both during the student period and during the professional period, and to do the profession by enjoying it, to adopt midwifery, and to contribute to innovations in the profession and to professionalize. Education is the primary condition for professionalization. Midwifery students should be educated about values and ethics during their education and training, meetings and seminars should be organized to develop their professional midwifery identity, and factors affecting their professionalism should be identified, and attempts should be made to let them improve their identities [15]. It is considered that midwives who will start working in their field thusly can make more positive contributions to the profession. In this study, it was found that there is a statistically significant difference between the grades of the students and the professional attitude towards the profession. The professional attitude scores of the sophomore and junior grade students were higher than those of the senior grade students [16]. This is because senior students may have disregarded professionalism because of their concerns about finding a job and not being able to fulfill the criteria for graduation [16]. In-service training should be organized to overcome the differences and inadequacies of midwives and nurses, which are two different professional groups, and professional promotions should be organized to create a positive image of midwives on social media. In conclusion, it is recommended that more cross-sectional and experimental studies be conducted to improve the professional identity of midwives.

References

1. Adıgüzel O, Tanrıverdi H, Sönmez Özkan D. (2011). Occupational professionalism and the case of nurses as the members of the profession. Yönetim Bilimleri Dergisi. 9: 39-59.
2. Sökmen Y, Taşpınar A. (2018). Professional attitudes of midwifery and factors affecting. Anadolu Journal of Nursery and Health Sciences. 24(2), 156-166.
3. Altıok HÖ, Üstün B. (2014). Professionalism: analysis of the concept. Dokuz Eylül University E-Journal of Nursery School. 7(2):151- 55.
4. Koçak YÇ, Can HÖ, Yücel U, Akyüz MD, Turfan EÇ. (2017). Academic and physical profiles of midwifery programmes in turkey. Journal of Health Sciences and Occupations. 4(2), 88-97.
5. Halldorsdottir S, Karlsdottir, SI. (2011). "The Primacy of The Good Midwife İn Midwifery Services: An Evolving Theory of Professionalism in Midwifery", Scand J Caring Sci. 25: 806–817.166.
6. Regulation on medical, nursery, midwifery, veterinary, pharmaceutics, and architecture faculties' minumum education conditions. T.C. Resmî Gazete, 26775, The second of February, 2008.
7. Regulation on job and job descriptions of health professionals and other professionals working in health services. Resmî Gazete, 22th of May 2014 Thursday, Volume: 29007. Adres: http://www.resmigazete.gov.tr/eskiler/20 14 /05/20140522-14- htm.
8. Reiger K. (2008). Domination or mutual recognition? Professional subjectivity in midwifery and obstetrics. Social Theory Health. 6:132-47.
9. Shaw HK, Degazon C. (2008). Integrating the core professıonal values of nursıng: a professıon, not just a career. 15(1):44-50.
10. Keeling J, Templeman J. (2013). An exploratory study: student nurses' perceptions of professionalism. nurse education in practice. 13:18-22
11. Bayındır Ü, Durak Hİ. (2008). Midwife workforce in turkey "current situation and 2013 vision". education and workforce planning in fields of medical health sciences in turkey. Interuniversity Council of Medical Health Sciences Education Council Presidency. 1-14.
12. Ersoy N. (2011) The importance of ethics in wifery and the reason why it is necessary. i. international & ii. national midwifery congress. Safranbolu, 12-14.
13. Öcek Z, Soyer A. (2007). Our data of primary health care services: 2003-2004 turkey viewing. Volume 1. Ankara: Turkish Medical Association Publishing. 23-25.
14. Merih YD, Arslan H. (2012). Job satisfaction levels of nurses and midwives and their ideas about professional awareness and professional organizations journal of education and research in nursery. 9 (2): 40-46.
15. Karaçam Z, Güleç T. (2016). The reasons of the new graduates and students mid wives introduce themselves as a nurse. Ege University Journal of Nursery Faculty. 32(2), 11-24.
16. Pınar ŞE, Cesur B, Duran Ö, Güler E, Üstün Z, Abak G. (2013). Analysis of occupational professionalism of midwifery students and affecting factors. Fırat Journal of Health Sciences. 8(23), 19-37.
17. Saydam BK. (2015). Midwifery in turkey as a professional occupation. health and society. 25(1):3-9
18. Çakaloz DK, Çoban A. (2019 Midwifery as a profession: what do postgraduate students think about? a one-state ase study. Anadolu Journal of Nursery and Health Sciences. 22(4), 240-249.

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Nurses' Views On Ethical Practices In Nursing Care: A Qualitative Study

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ABSTRACT

Nurses are required to make ethical decisions with the ethical principles of the nursing profession while making decisions in clinical practice. Therefore, it is very important to recognize and solve ethical problems. The purpose of this research is to learn in-depth the views of nurses about ethical practices and nurses' behavior towards individuals when giving care.

A hermeneutic-phenomenological qualitative study was performed. Qualitative data were gathered through semi-structured in-depth interviews from March to November 2020 four hospital in Kocaeli. This qualitative study was carried out with the data collected in face-to-face, in-depth interviews with a semi-structured questionnaire. Interviews were conducted with 40 nurses, each taking 30–60 min. The obtained data were evaluated with the inductive content analysis method.

Content analysis of the interview based on nurses' descriptions revealed four major themes. Themes: The meaning given to care ethics, difficulties encountered in nursing care, ethical values in nursing care and ethical approach of hospital management. The nurses indicated that their level of care ethics knowledge was insufficient, and they needed to receive comprehensive ethical care training from a qualified specialist. In addition, nurses' personal characteristics, religious and cultural values, and professional experiences were found to be factors affecting nursing care. It was also found that the support and motivation of nurses by their managers positively affected their care.

In the interviews, nurses consider it necessary to provide care by paying attention to ethical behaviors in nursing care and practices for the development and professionalism of the profession, but they state that they do not have an idea about how this will be provided. It was determined that nurses thought that more attention should be paid to the importance and value of ethics in nursing interventions, and ethical practices in nursing care should be included in in-service training programs.

Keywords: Nursing ethics, nursing care, ethical practices

Hemşirelerin Hemşirelik Bakımında Etik Uygulamalara İlişkin Görüşleri: Niteliksel Bir Araştırma

Süreç

Geliş: 18/01/2023
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ÖZ

Hemşirelerin klinik uygulamada karar verirken hemşirelik mesleğinin etik ilkelerine uygun olarak etik kararlar alması gerekmektedir. Bu nedenle etik sorunların tanınması ve çözülmesi oldukça önemlidir. Bu araştırmanın amacı hemşirelerin etik uygulamalara ilişkin görüşlerini ve hemşirelerin bakım verirken bireylere yönelik davranışlarını derinlemesine öğrenmektir.

Hermenötik-fenomenolojik nitel bir çalışma gerçekleştirildi. Niteliksel veriler Mart-Kasım 2020 tarihleri arasında Kocaeli'deki dört hastaneden yarı yapılandırılmış anket formu ile toplanmıştır. Bu nitel çalışma yüz yüze derinlemesine görüşmelerde toplanan verilerle gerçekleştirilmiştir. Görüşmeler 40 hemşire ile gerçekleştirildi ve her görüşme 30-60 dakika sürdü. Elde edilen veriler tümevarımsal içerik analizi yöntemiyle değerlendirilmiştir.

Hemşirelerin açıklamalarına dayalı olarak yapılan görüşmelerin içerik analizi dört ana temayı ortaya çıkardı. Temalar: Bakım etiğine verilen anlam, hemşirelik bakımında karşılaşılan zorluklar, hemşirelik bakımında etik değerler ve hastane yönetiminin etik yaklaşımlarıdır. Hemşireler, bakım etiği ile ilgili bilgi düzeylerinin yetersiz olduğunu ve alanında uzman bir kişiden kapsamlı bakım etiği eğitimi almaları gerektiğini belirtmişlerdir. Hemşirelerin kişisel özellikleri, dini ve kültürel değerleri ve mesleki deneyimleri de hemşirelik bakımını etkileyen faktörler olarak saptanmıştır. Ayrıca hemşirelerin yöneticileri tarafından destek ve motivasyonunun bakımlarını olumlu yönde etkilediği bulunmuştur.

Görüşmelerde hemşireler, mesleğin gelişimi ve profesyonelliği için hemşirelik bakımında etik davranışlara ve uygulamalara dikkat ederek bakım verilmesinin gerekli olduğunu düşünmekte ancak bunun nasıl sağlanacağı konusunda fikir sahibi olmadıklarını belirtmektedirler. Hemşireler, hemşirelik girişimlerinde bakım etiğinin önemine ve değerine daha fazla önem verilmesi gerektiğine ve hemşirelik bakımında etik uygulamalara hizmet içi eğitim programlarında yer verilmesinin çok önemli olduğuna dikkat çekmektedir.

Anahtar sözcükler: Hemşirelik etiği, Hemşirelik bakımı, Etik uygulamalar

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Introduction

Nursing care is the primary role unique to nursing [1]. The feature that makes nursing care privileged is its awareness and sensitivity about the moral aspect of care and its reflection on the patient-nurse relationship by combining it with professional knowledge and skills [1, 2]. Nursing care is the ability of a nurse to combine and present their correct knowledge, practical intelligence, judgment, and specialized psychomotor skills in line with ethical principles and professional values [3, 4]. Medical errors due to lack of knowledge and skills, poor decision-making and problem-solving ability, negligence, or carelessness cause severe problems in individuals [5]. Even these problems can end the life of an individual. Incorrect drug administration to a patient, injecting a drug into the artery instead of a vein, administering too much medication without calculating the dose, and administering high insulin doses to people with diabetes are examples of errors that can cause serious problems. Medical errors are against patient rights and ethical principles as they result in harm to individuals. It causes a decrease in patient safety and quality of care [2, 6]. For this reason, nurses should be aware of their moral responsibilities while providing care and be more sensitive to the care needs of individuals [6].

The concept of care ethics is to determine the specific needs of patients by nurses and meet them following ethical principles. For babies who need nursing care; small children; individuals with mental or physical disabilities; bedridden, conscious or unconscious patients; patients living in emergency care, intensive care, and operating rooms have a high risk of vulnerability, as they have weak capacity to think and make choices about their care, restricted movements, vulnerable, and need to protect their privacy [7, 8, 9]. Nurses should display more sensitive ethical care behaviors in line with the values and needs of the patient during their care.

For this reason, nurses must recognize ethical problems and provide solutions; It is necessary to determine how much they perform autonomous, respectful, and sensitive nursing care practices. In this context, it is aimed to bring individuals into complete well-being by evaluating them physically, mentally, socially, and psychologically. Determining the behaviors of nurses towards care ethics in the protection and improvement of the health of individuals will contribute economically to the disease burden. The purpose of the study was to determine the ethical challenges and dilemmas encountered by nursing care and examine nurses' professional ethical behavior.

Methods

1. Study Design

A hermeneutic-phenomenological qualitative study was performed. A qualitative study examined nurses' views on care ethics and their ethical behavior in patient care. The study was conducted through face-to-face in-depth interviews with a semi-structured questionnaire. Content analysis was considered a research method for reaching the concepts that can explain the data and the relationships between concepts.

2. Sample and Participants

Qualitative data were gathered through semi-structured in-depth interviews from March to November 2020, four hospital in Kocaeli. Nurses were sampled from those who work designated units, and inclusion criteria are working in internal or surgical clinical sciences for at least two years, aged 22 years or above, and willing to consent to and participate in in-depth interviews. The nurses have accepted sampling from those who work to take care of patients in four hospitals from Turkey. They participated in an interview conversation by contacting the leader of these nurses. If the nurses were willing to attend interview conversations and talk about their views and behavior about care ethics, they were asked to sign a written consent form. Forty nurses consented to participate in this study. Interviews were conducted with 40 nurses and each interview took 30–60 min. A preliminary interview was held with five nurses, the draft of the interview was made more precise and logical. Then, other nurses were included in the sample, respectively.

3. Data Collection Tools

Interview outline for open-ended questions was drafted with experts specializing in nursing care, nursing management, and nursing education. According to the pre-interview results, the final interview outline was created. The main questions were the following:

1. *What are your views on nursing care?*
2. *Do you have any ethical challenges while applying nursing care?*
3. *How did you cope with these ethical challenges?*
4. *Do you have situations where you have an ethical dilemma during nursing care?*
5. *What are the ethical behaviors to be considered while applying nursing care?*

4. Data Collection

Qualitative data were gathered through semi-structured in-depth interviews from March to November 2020. In this study, the phenomenology

method, one of the qualitative research methods, was used to comprehend the nurses' personal views and perspectives on nursing ethics and ethical care behaviors as a holistic. In-depth interviews are a data collection technique covering all dimensions of the subject under investigation; mostly open-ended questions are asked, detailed answers are obtained, and information is collected through face-to-face interviews.

Firstly, researchers explained to the participants the purpose of the study, voluntary participation, data confidentiality, and qualitative interviewing. Then, during the interviews, it was said that a tape recorder would be used, and permission was obtained from the participants. All interviews were conducted in a meeting room at the hospital where the participants work. Each interview took 30–60 min, and the average time was 45 min. In this study, researchers conducted 40 interviews, including five pre-interviews 35 formal interviews. Pre-interviews were conducted before the formal interviews to ensure accuracy and the interview outline's rationality. After the five interviews, researchers analyzed the texts to follow up on subsequent interviews, critically examine the interviews, and explore themes. This process was repeated with all researchers participating after five interviews. The statements were recorded after each interview. It was transcribed verbatim after listening to this recording, with non-verbal information included. The transcribed data was read thoroughly several times by the researchers, followed by an analysis of each interview as a single text.

5.Data Analysis

All interviews were transcribed, the researchers analyzed first separately, then each interview as single texts; this process was repeated with researchers after all interviews. Completed texts were then explored as a whole, analyzing each interview for the entire text. The questions in the study are used as a guide for conducting the analysis. The obtained data were evaluated through the content analysis method. The primary purpose of content analysis is to reach the concepts and relationships that can explain the collected data [10, 11]. Inductive content analysis, which consists of 4 stages: coding data, finding themes, organizing and defining them according to given codes and themes, and interpreting the findings, was used to organize the data. Collected data is codified and classified into words, sentences, or paragraphs. The themes occurred after the gathered data had been coded and categorized to see the whole. The propositions emerging from the study were made according to the themes.

Ethical Considerations

This study was approved by the University Research Ethical Committee (approval number 20.06.2019-133). Participants were provided with written and oral information. Then the aim of the study was explained. Before every interview, information was given about the interview and registration procedures. It was repeated that they had the right to withdraw from research whenever they wanted. If participants gave voluntary consent, they were invited to sign the consent form before participation in the study. All data are confidentially treated.

Results

A total of 40 eligible nurses were accepted to study, aged 22–45 years and had a nursing tenure of 2–25 years. They shared the ethical challenges of caring for patients and their ethical decision-making (Table 1).

Four main themes emerged in this study, namely the meaning given to care ethics, difficulties encountered in nursing care, ethical values in nursing care and ethical approachs of hospital management.

1. The meaning given to care ethics

In the one-to-one interviews with nurses, almost all said that care should be given within ethical codes. They stated that the primary responsibility of nurses is for individuals who need nursing care and that care should be given in a way that respects the rights, culture, values, and beliefs of the individual, the family, and the community. They also emphasized that the nurse should inform the patient and get permission before care practices, keep the patient's personal information confidential, and defend equality and justice in individuals' access to health services. Most importantly, they stressed the need for comfortable care in conscience.

"You are alone with your conscience!"

"I think you are ethically alone in the intensive care unit with your conscience. If I do not make the patient's antibiotic, no one knows about it if I throw away the prescription. Because when we come on duty, we share patients, and then we start our nursing care, no one touches my patient but me." (N10)

Some of the nurses mentioned that the care would be better by providing an empathetic approach to the care of the patients.

"When you think of nursing care like your own family, your care is quality. Because in my professional life, I applied my care by thinking as if my parents." (N17)

Table 1. Socio-Demographic Characteristics Of The Participants

Table 1. Socio-Demographic Characteristics Of The Participants

Gender	**n**
Female	35
Male	5
Age	
22-29	17
30-37	7
38-45	16
Education Level	
Health vocational high school	4
Associate degree	4
Bachelor's degree	30
Master's degree and higher	2
Work Experience (years)	
2-5	13
6-10	9
11-15	2
≥ 16	16
Clinical area	
İnternal medicine/Surgery department	22
İntensive care unit/ Reanimation unit	11
Orthopedic/Traumatology department	7

2. Difficulties encountered in nursing care

As a result of the conflict of ethical values and responsibilities while providing health services in hospitals, nurses often face ethical dilemmas with nurse-patient, nurse-physician, nurse-patient relative, nurse-other health professionals in the service procurement process.

Experienced difficulty caring for the other sex

Nurses mentioned that proper care should be given to everyone without gender discrimination in the care of patients. However, some nurses stated that they had difficulties giving care to patients of the opposite sex; they did not want to give care while providing nursing care.

"It is necessary to give equal care to everyone, regardless of whether they are men or women. However, I have a hard time caring for men. For example, it is very difficult for me to insert a urinary catheter and take a urine culture in male patients." (N4)

Requesting privileged care

From the data, this theme emerged when higher authorities working in the hospital were asked to provide privileged care according to the socio-economic level of some patients from the nurses.

"There should be a special room requirement according to the patient's needs and the surgery situation. I do not think it is necessary to give a private room to the person who pays. Or he has donated to the service and has all his relatives look after him. As soon as an ordinary outside patient comes in, I think these are unethical." (N28)

The image of nursing in society

The participants defined that they saw nurses as miraculous and thought we would heal every patient. They also mentioned that false information learned from social media complicates nursing care.

"Social media has been making our job very difficult lately. This is how my friends think. There are also misrepresentations in TV series. They see us as superman as if everything is in our hands. Some things tie our hands. We cannot do everything. We seem to have a magic wand in our hands. This time, we are in a difficult situation when the patient cannot recover. We are also exposed to the interventions of patients and their relatives. People judge us with false and false information from social media. While they are going to support us, they become a hindrance. Moreover, we try to tell them our problem." (N1)

Difficulties in communication with the team, patient and patient relatives

There were disruptions in nursing care and practices because of the inability to provide therapeutic communication with patients and their relatives.

"For example, I have a patient right now, and I have much trouble with his care. For example, I could not open the vascular access, I could not get blood, the relatives of the patients are not oriented, I try to help, but patients and their relatives are not oriented. You cannot care for a patient who does not want it anyway; you cannot care for him if he does not join you." (N16)

Difficulties in the treatment of patients

The nurses are shy in the treatment of the patients, refusal of the patients to receive the treatment, or even if the patients do not give written consent, the willingness of the patients to treatment causes some difficulties in the treatment of patients.

"There are treatments for which we need consent from patients. We have patients who do not want to give consent but want to receive that service even though they do not give consent. They want us to take full responsibility, and they want us to be held accountable in cases where accountability is required." (N10)

3. Ethical Values in Nursing Care

Nurses, who are in constant communication with the patient in health care and treatment, frequently encounter ethical problems while fulfilling their roles such as treatment, care, education and counseling. Among the problems that nurses have ethical dilemmas are; Patient safety is experienced when making decisions in patients' health services and care, giving care in accordance with the values and beliefs of patients.

The importance of patient safety

Participants talked about the importance of patient follow-up in preventing drug administration errors.

"I think communication, privacy, the right medicine, the right patient, the right time are very important. In crowded wards, the wrong drug may be administered to the wrong patient, and I think this needs to be taken very seriously and should be controlled a lot. For example, they taught us at the university that you will look at the medicine, look at the patient's wristband, and confirm the patient separately. I think this is a hundred percent proper application." (N16)

Situations with an ethical dilemma

Some participants stated that they had difficulty deciding whether the patients had pain and applied a placebo not to give painkillers to the patients.

"I have a dilemma when applying nursing care; for example, there are painkillers. For example, does the patient have pain? I am torn between taking the patient's pain reliever or not. For example, the patient receives paracetamol, even if it is not necessary, I ask the patient. Or I think whether to do it in anticholinergic or not." (N8)

The effect of nurse's experience on decision making

The participants mentioned that they made decisions about the patient easier with the knowledge of their professional experience.

"In the first ten years I started working, there were situations where I was indecisive, but after the first ten years, I did not encounter any. Although I have been a nurse for 26 years, I always ask. Moreover, on top of that, I easily apply what I know so that no one can tell me anything." (N15)

Participants new to the profession mentioned that they were in a dilemma, hesitations, and avoidance of care due to the lack of professional knowledge and skills.

"I started my profession six months ago, and I do not know what to do; for example, I do not know how to care for diabetic foot. I cannot decide because I do not know." (N16)

Respect for values and beliefs

Participants explained that they experienced difficulties in religious rituals such as hair and beard and that patients refused treatment due to the content of the drug.

"Although very rare, we have some difficulties with the relatives of the patients. For example, they do not want patients' hair and beard to be cut. We have the most problems in cutting hair and beard." (N5)

"For example, the patient does not want blood thinners or insulin. There is a pig's oil in the blood thinner; he does not want to have the blood thinners because of his religious denomination. This patient is a post-op patient. Neither did we." (N28)

4. Ethical approachs of hospital management

Ethical dilemmas are experienced due to the gaps in the job descriptions of nurses, the inadequacy of the number of staff and nurses, and the problems arising from the lack of support systems of the administrators.

Lack of support of nurses

The participants stated that the management and managers do not support the nurses in case of any complaints, and at the same time, the nurses do not support each other.

"The relatives of the patients complain; the relatives of the patients are right in every way, and you do not have the right to rest and explain the incident; it is as if we are wrong in every way. Complaints are perceived as a success by patients." (N38)

"It would be better if there was no jealousy among the nurses; I would work more peacefully and actively. I am unmotivated, want to be honored,

want to be rewarded; these are more constructive things. Shifts are arranged according to personal relationships, or when mistakes are made, the nurse in charge does not alert those whose personal relationship is good." (N28)

Definition of duties, authorities, and responsibilities

The participants stated that patient care was interrupted due to non-nursing jobs (such as secretariat, reports to be placed in the patient file, and many documents) that are not intended for one-on-one patient care, and the insufficient number of nurses compared to the number of patients.

"Our workload is too much. That is why I cannot provide psychological support and deficiencies enough to the patients. We have all the responsibilities. We support services; we have the secretarial job, sometimes we do the cleaning. We were supposed to refer a patient the other night, but I do not know. No secretary at night. I called many people until I referred the patient, I did, but I neglected the care of other patients." (N4)

Discussion

This study aimed to determine the care ethics behaviors of nurses in their care and practices and explain their thoughts on care ethics. The analysis generated four themes.

In the interviews, nurses consider it necessary to provide care by paying attention to ethical behaviors in nursing care and practices for the development and professionalism of the profession, but they state that they do not have an idea about how this will be provided.

Ethical sensitivity, defined as the ability to distinguish ethical problems, needs to be developed for nurses to recognize and solve ethical problems and make correct decisions. Considering the studies, it is seen that nurses are in an effort to provide ethical care to the patient and their family, but they are not enough [12, 13, 14]. In the study conducted by Yıldırım et al., it was determined that nurses are in an effort to provide care in accordance with ethical principles, but they have difficulty in fulfilling their ethical obligations due to the health problems they experience, professional, ethical and moral problems [14]. Similarly, in other studies, it was determined that most of the nurses had ethical problems and could not solve this problem, and they received help from the responsible nurse to solve this problem [15, 16]. In a study conducted with nurses in South Korea, it was determined that the uncertainty of right and wrong actions in order to maintain good nursing caused nurses to violate ethical principles due to the conflict of ethical values and nurses' own values [13]. In the 2020 study of Haahr et al., it is stated that nurses try to provide care by being aware of their ethical obligations to the patient and their family, but they need to be supported [12]. In this study, it was stated that nurses are aware of their professional ethical obligations and it is important to fulfill ethical obligations. The findings of the study were similar to the results of the literature, and it was stated that in the majority of the studies, nurses had ethical problems and that they could or could not solve this ethical problem with help. This situation shows the necessity of training of nurses especially for ethical decision making process. It is thought that including this subject in in-service training programs will contribute positively to the decision-making process.

Özyer's study found a significant relationship between ethical attitudes and various demographic factors (such as age, gender, education, occupation, belief), and that demographic characteristics affect ethical behaviors [17]. When the literature is examined; In the study of Tosun [18] 72.4% of the nurse group had a professional working period of 1-10 years, in the study of Dalcalı [19] 28.8% of the nurses were between 11-15 years and Aslan in their study [20] , it was determined that 51.85% of the nurses were between 5-10 years. In the findings of these studies, it is reported that the nurses do not have the ability to critically evaluate the care provided to meet the personal care needs of the patients from an ethical perspective, due to the fact that the majority of the nurses constitute the young nurse group. Similarly, in the study of Başak et al. and Dikmen [15, 21], age and duration of clinical experience are important factors in gaining ethical sensitivity, in the study of Kahriman and Çalık [22], they found that 36-year-old nurses had higher ethical sensitivity than 25-year-old nurses. A nurse with sufficient knowledge and experience quickly develops solution skills during the evaluation phase of the existing ethical problem [23, 24]. In this study, it was found that increasing age and working experience positively affected ethical behaviors. In order to provide quality nursing care, besides professional experience and age, nurses should act according to the principles of correct behavior.

It was thought that nurses in the young age group had a short working time in the profession, did not have experience, and therefore the number of encountering ethical problems was low, and they might be insufficient in recognizing ethical problems. Similarly, in studies conducted to determine the moral sensitivity of young intensive care nurses in Turkey, it was determined that the age factor had an effect on moral sensitivity [25,

26]. In Arslan's study, it was concluded that nurses who are young and new to the profession are mostly in ethical dilemmas and this is due to a lack of self-confidence [27]. In another study, it was determined that nurses who have been working for less than a year have lower moral sensitivity than experienced nurses [15, 28]. There are also studies that concluded that lack of professional experience is one of the obstacles to the development of moral sensitivity in nursing [29]. In this study, the fact that the nurses in the young age group participating in the research have not yet faced the problems that require ethical decision making or that they have not reached a sufficient level of awareness affect their ethical decision making. On the other hand, as the time spent by experienced nurses in the profession increases, they can make decisions more easily because they encounter too many ethical problems.

As professional members, nurses have undertaken the responsibility of providing adequate and qualified care to society. While the nurses provide the care they deem appropriate for the patient's benefit in line with the principle of providing benefit, ethical problems arise from the issues related to the patients [30]. While the key role of the nursing profession in maintaining the health of individuals and society cannot be denied, it has been reported that unfortunately it has not gained the value and respect it deserves [31, 32, 33]. It has been reported that one of the most important factors in not seeing the value that the nursing profession deserves is the social professional image, and the other is the professional image of the professionals [33, 34]. In this study, the provisions regarding the duties, authorities and responsibilities of the nurse in the current legislation are not fully known by the nurses, their teammates and the society. When the social nursing image towards the nursing profession is examined in the researches; The fact that the nursing profession is a knowledge and skill-based profession that has an important place in public health, [32, 35] on the other hand, in the study of Morcinowicz et al., [36] the fact that anyone who cares for people can be a nurse indicates that they perceive the nursing profession as a simple job. indicator. However, it has been reported that it is important for healthcare team members to know each other's roles and their importance in the team, to establish mutual open and respectful communication, and to use their autonomy for patient health [37]. When the social nursing image researches on the role of nurses are examined; The participants perceived the functions and duties of the nurse mainly in the categories of diagnosis, treatment and application of auxiliary procedures given by physicians [35, 36, 38]. However, it has been reported that misleading messages about the duties of nurses are given in the media [39]. For all these reasons, it was thought that the awareness of the nurses' duties was insufficient in the society and that the society perceived the nursing profession as an auxiliary profession that fulfills the assigned duties.

Nurses complain that there are too many different attitudes and no certain standard because ethical principles and values are not reinforced during their care and practices. Due to the lack of a standard, it has been concluded that the quality of caregiving varies from nurse to nurse; personal values come before professional values, which damages the image of professional dignity. It has been observed that the quality of the interventions applied to the patient in each nurse who changes in different shifts in the profession that operates according to the shift method, is changing according to the output as a result of the personal decision mechanisms, leaving the professional knowledge and skill standards obtained during the training. In studies in which the ethical sensitivities of nurses are discussed according to their working style, it is seen that the general ethical sensitivities, autonomy, benefit and holistic approach ethical sensitivities of nurses working in shifts are higher than those of nurses who constantly work during the day [40, 41]. On the other hand, in the studies of Öztürk et al., it was determined that the way of working in nurses was not related to ethical sensitivity[42]. Nurses undertake many responsibilities regarding nursing practices within the scope of their duties. In this context, it can be explained by the fact that nurses who work in shifts feel the sense of responsibility they carry more intensely due to the fact that they work with fewer team members during the shift period compared to nurses who work constantly during the day, and accordingly they show higher ethical sensitivity. In order to prevent this situation, an opinion has been expressed as follows: It has been determined that it is complicated to create change on an individual basis to gain ethical behavior, and it is possible to make a radical change with the corporate culture.

Conclusion

Nursing is based on professional philosophy and a scientific ethics. Ethical care is very effective on nursing care practices. Ethical care depends on the ability to act in line with ethical principles in the decision-making process in the face of problems. In this study, it was revealed that nurses had difficulties solving ethical problems. It is stated that more than half of the nurses participating in the study have difficulties solving problems despite

receiving training on ethics. In this case, ethics committees should be established in institutions where the nursing profession is practiced, nurses should be included among the board members, hospital management protocols should be created by managers so that nurses recognize and evaluate ethical principles and professional organizations should give due importance. It has been stated that nurses' characteristics such as conscience, positive relations with others, self-control skills and sense of responsibility, communication skills, and awareness of responsibility can also affect ethical behaviors.

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Conflicts of interest
The authors declare that they have no conflict of interest.

Limitations
In this study, it can be taken into account that the participants did not adequately report their nursing care practices or they may have misreported some behaviors that they actually did but thought were unacceptable.

Authors Contributions
Author 1: research idea, design of the study, acquisition of data for the study, analysis of data for the study, interpretation of data for the study, drafting the manuscript, revising it critically for important intellectual content, final approval of the version to be published
Author 2: research idea, design of the study, interpretation of data for the study, drafting the manuscript, revising it critically for important intellectual content, final approval of the version to be published

Ethical approval
This study was approved by Ethics committee of 20.06.2019-133.

References

1. Baykara ZG. The concept of nursing care. TJOB 2014;1(2):92-99.
2. Dinç L. The concept of caring and its' moral component. Hacettepe Univ Faculty of Health Sciences J 2010; 74-82.
3. Elçigil A, Bahar Z, Beşer A, Mızrak B, Bahçelioğlu B, Demirtaş D, Özdemir D, Özgür E, Yavuz H. Ethical dilemmas which are faced by nurses. J Nursology 2011; 14(2):52-60.
4. Riggio ER, Taylor JS. Personality and communication skills as predictors of hospice nurse performance. JBP 2000; 15(2):351-359.
5. Cortis JD, Kendrick K. Nursing ethics, caring and culture. Nurs Ethics 2003; 10:77-88.
6. Ağaçdiken S, Aydoğan A. Empathic skills and ethical sensitivity relationship in nurses. Gumushane Univ J Health Sciences 2017; 6(2):122–129.
7. Held V. The ethics of care: personal, political, and Global. In: Care and Moral Theory, Oxford University Press 2006, p. 9-29.
8. Dinç L. The importance of ethics of care for nursing practice. Turkish Clinics J Med Ethics Law Hist-Special Topics 2017; 3(1):1-9.
9. Vanlaere L, Gastmans C. A personalist approach to care ethics. Nurs Ethics. 2011;18(2):161-73.
10. Ngulube P. Qualitative data analysis and interpretation: systematic search for meaning. In. Mathipa ER, Gumbo MT (Eds) Addressing research challenges: making headway for developing researchers. Noordywk: Mosala-MASEDI, 2015; pp 131-156.
11. Yıldırım A, Şimşek H. Qualitative research methods. In: Yıldırım A, Şimşek H (Eds) Qualitative research methods in social sciences. 5nd ed. Ankara: Seçkin Publications, 2016; pp 232-266.
12. Haahr A, Norlyk A, Martinsen B, Dryer P. Nurses experiences of ethical dilemmas: A review, Nurs Ethics 2020; 27(1):258-272.
13. Kim M, Oh Y, Kong B. Ethical conflicts experienced by nurses in geriatric hospitals in South Korea: "If You Can't Stand the Heat, Get Out of the Kitchen". IJERPH 2020; 17(4442):2-13.
14. Yıldırım B, Gerçek E, Karabudak SS. The problems of nurses working in the newborn intensive care unit: A Qualitative Research. J Adnan Menderes Univ Health Sciences Faculty 2020; 4(2):144-153.
15. Başak T, Uzun Ş, Arslan F. Investigation of the moral sensibility of intensive care nurses. Gulhane Med J 2010; 52:76-81.

16. Aksu T, Akyol A. Investigation of the moral sensibility of nurses in İzmir. Turkiye Klinikleri J Med Ethics 2011; 19(11):16-24.
17. Özyer K, Azizoğlu Ö. The impacts of demographic variables on people's ethical attitude. IJESR 2010; 6(2):59-84.
18. Tosun H. Determining the Sensitivity of Physicians and Nurses to Ethical Dilemmas Experienced in Health Care Practices. Istanbul: Istanbul Univ; 2005.
19. Dalcalı KB, Şendir M. Determining the relationship between nurses personal values and their ethical sensitivity. Florence Nightingale J Nurs 2016; 24(1);1-9.
20. Aslan Ö, Vural H, Avcı PY. Determination of operating room nurses' approaches to ethical problems. Gulhane Med J 2003; 45(2):147-152.
21. Dikmen Y. An observation on the moral sensibility of intensive care nurses. Cumhuriyet Nurs J 2013; 2(1):1-7.
22. Kahriman İ, Çalık KY. Ethical sensitivity of clinical nurses. Gumushane Univ J Health Sciences 2017; 6(3):111–121.
23. Burkhardt AM, Nathaniel AK. Ethical Priciples. In: Alpar ŞE, Bahçecik N and Karabacak Ü (Eds). Ethics Issues in Contemporary Nursing. 3nd ed. İstanbul, Istanbul Tip Kitapevi, 2013; pp 52-78.
24. Grace PJ. Nursing ethics and professional responsibility in advanced practice.In.Gaylord NM (Eds). Ethical Liedership by Advanced Practises Nurses. 3nd ed. Burlington, Massachusetts: Jones and Bartlett Learning; 2018; chap 5.
25. Aytaç N, Naharcı H, Öztunç G. Knowledge about nozocomial infections of nurses working in intensive care in training and research hospitals in Adana. Journal of Adnan Menderes Univ Med Faculty 2008; 1(3):9-15.
26. Çelen Ö, Karaalp T, Kaya S, Demir C, Teke A, Akdeniz A. The considerations about and expectations from in-service training programs of the nurses working at the intensive care units of the education hospital of gulhane military medical faculty. Gulhane Med J 2007; 49(1):25-31.
27. Arslan G. The İmpact Of Nurse's Ethical Sensitivity Levels On Their Approaches To Ethical İssues Spesific To İntensive Care. Istanbul: Acıbadem Mehmet Ali Aydınlar Univ; 2017.
28. Kulju K, Suhonen R, Leino KH. Ethical problems and moral sensitivity in physiotherapy: A Descriptive Study. Nurs Ethics 2013; 20(5):568-577.
29. Huang FF, Yang Q, Zhang J, Khoshnood K, Zhang JP. Chinese nurses 'perceived barriers and facilatators of ethical sensitivity. Nurs Ethics 2016; 23(5):507-522.
30. Demirsoy N, Yılmaz AT, Şaylıgil Ö. Nurses' approaches to ethical dilemmas: An example of a public hospital. JHS 2018; 15(3):1568-1583.
31. Eşer İ, Orkun N, Çetin P. The image of nursing and a series of advertisements published in the 1950s. DEUHFED 2017; 10(4):275-278.
32. Çelik As, Pasinlioğlu T, Kocabeyoğlu T, Çetin S. Determination of the image of nursing profession in community. Florence Nightingale J Nurs 2013; 21(39):147-153.
33. Derin N, Ilkım NŞ and Yayan H. Expression of professional adherence by professional prestige in nurses. Hacettepe Univ Faculty of Health Sciences J 2017; 4(3):24-37.
34. Crawford P, Brown B, Majomi P. Professional identity in community mental healty nursing: a tehematic analysis. IJNS 2008; 45:1055-1063.
35. Meiring A, Van Wyk NC. The image of nurses and nursing as perceived by the south african public. AJHNM 2013; 15(2): 3–15.
36. Marcinowicz L, Foley M, Zarzycka D, Chlabicz S, Windak A, Buczkowski K. Polish medical students' perceptions of the nursing profession: A cross-sectional study. Scand Journal Caring 2009; 23:438–445.
37. Öğüt A, Kaya D. Teamwork in healthcare organizations. Selcuk University J Social and Technical Researches 2011; 1(1):88-95.
38. Keçeci A, Durmuş SÇ, Oruç D, Kapisiz ÖÖ. The society's view of nursing in Turkey. Hospital Topics 2014; 92(2):36– 43.
39. Ertem G, Dönmez YC, Oksel E. Investıgatıon of nursıng news in daily Turkish newspapers. Maltepe University J Nurs Science and Art 2009; 2(2):70-75
40. Kavak ŞN. Investigation Of Ethical Sensitivity And Burnout Levels Of Nurses. Istanbul:Usküdar Üniv; 2020.
41. Dezhkam L, Kargar Z, Kalani N, Tafvizi MD, Jahromi HK. The study of moral sensitivity of fasting nurses working in therapeutic educational hospitals of jahrom. International J Med Research & Health Sciences 2016; 5(7):158-165.

42. Öztürk EA, Şener A, Koç Z, Duran L. Factors ınfluencing the ethical sensitivity of nurses working in a university hospital. Eastern J Med 2019; 24(3):257-264

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Knowledge Levels, Attitudes and Behaviors of Pregnants About Prenatal Screening Tests: A Sectional Study

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ABSTRACT

To determine the knowledge levels, attitudes, and behaviors of pregnant women who come to the obstetrics clinic in a university hospital about prenatal screening tests.

It is a descriptive cross-sectional study. The population comprises approximately 900 pregnant women aged 28 weeks and beyond who applied to the Sivas Cumhuriyet University Faculty of Medicine, Obstetrics and Gynecology outpatient clinic between October and December 2021. The research questionnaire was used face-to-face with those who agreed to participate. The data form consisting of 21 questions included questions about pregnant women's descriptive characteristics and obstetric histories.

254 people participated. The mean gestational week of the participants was 34.9±3.9 (min:28-max:41). The most common screening tests were detailed ultrasound (80.7%) and double screening tests. Those who received information from their obstetrician had a significantly higher rate of having the difficulty. When the participants' knowledge scores about prenatal screening tests are evaluated, respectively, the Detailed ultrasound knowledge score was 5.6±0.9, Double test 5.0±1.3, Oral Glucose Tolerance Test(OGTT) 4.8±1.1, and Triple test 4.7±1.2(min:2-max:7). When the reasons for not having prenatal screening tests were questioned, the most common answer for all screening tests was "I don't think the test is necessary." For the OGTT, the second most common reason for not having it done was because they heard from the media that the test was harmful. The fact that the pregnant women who had a double and triple screening went to regular controls and had a high double-triple test knowledge score had a significant effect. Amniocentesis was recommended for 3.5% of the pregnant women based on prenatal test results, but none had amniocentesis. In case of unfavorable prenatal test results, most pregnant women were considering continuing the pregnancy.

In this study, we found that the testing rate increased with the increasing knowledge level of pregnant women and physician counseling. In this context, health professionals should provide women with the necessary education about screening and diagnostic tests to enable them to make informed decisions.

Keywords: Prenatal, Screening Test, Pregnant, Knowledge, Prenatal Screening Test

Gebelerin Doğum Öncesi Tarama Testleri Hakkında Bilgi Düzeyleri, Tutumları ve Davranışları: Kesitsel Bir Araştırma

Süreç

Geliş: 07/06/2023
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ÖZ

Bu çalışmada amaç; bir üniversite hastanesinde kadın doğum polikliniğine başvuran gebelerin doğum öncesi tarama testleri hakkındaki bilgi düzeyleri, tutum ve davranışlarını belirlemektir.

Tanımlayıcı kesitsel bir çalışmadır. Evreni Ekim-Aralık 2021 tarihleri arasında Sivas Cumhuriyet Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum polikliniğine başvuran 28 hafta ve üzeri yaklaşık 900 gebe oluşturmaktadır. Araştırmaya katılmayı kabul edenlere araştırma anketi yüz yüze uygulanmıştır. 21 sorudan oluşan veri formu, gebelerin tanımlayıcı özellikleri ve obstetrik öykülerine ilişkin sorular içermektedir.

254 kişi katıldı. Katılımcıların ortalama gebelik haftası 34,9±3,9(min:28-max:41) idi. En yaygın tarama testleri ayrıntılı ultrason (%80,7) ve ikili tarama testleri idi. Kadın doğum uzmanından bilgi alanların testi yaptırma oranı önemli ölçüde daha yüksekti. Katılımcıların doğum öncesi tarama testleri hakkındaki bilgi puanları değerlendirildiğinde sırasıyla; Ayrıntılı ultrason bilgi puanı 5,6±0,9, İkili test 5,0±1,3, Oral Glikoz Tolerans Testi (OGTT) 4,8±1,1 ve Üçlü test 4,7±1,2(min:2-maks:7) idi. Doğum öncesi tarama testi yaptırmama nedenleri sorgulandığında tüm tarama testleri için en yaygın yanıt "Testin gerekli olduğunu düşünmüyorum" oldu. OGTT 'de ise ikinci sıklıkta yaptırmama nedeni, testin zararlı olduğunu medyadan duymalarıydı. Gebelerin ikili ve üçlü tarama yaptırmış olması, düzenli kontrollere gitmesi ve ikili üçlü test bilgi puanının yüksek olması anlamlı etki göstermişti. Prenatal test sonuçlarına göre gebelerin %3,5'ine amniyosentez önerildi, ancak hiçbirine amniyosentez yapılmadı. Doğum öncesi test sonuçlarının olumsuz çıkması durumunda gebelerin büyük çoğunluğu gebeliğe devam etmeyi düşünmekteydi.

Bu çalışmada gebelerin bilgi düzeyi ve hekim danışmanlığı arttıkça tarama testi yaptırma oranlarının arttığını bulduk. Bu bağlamda sağlık profesyonelleri, kadınlara bilinçli kararlar verebilmeleri için tarama ve tanı testleri konusunda gerekli eğitimi vermelidir.

Anahtar sözcükler: Doğum Öncesi, Tarama Testi, Gebe, Bilgi, Doğum Öncesi Tarama Testi

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Introduction

Prenatal care (PNC) is essential to improve infant health outcomes such as timely delivery and average birth weight. One of the goals of PNC is to identify women whose fetuses are at risk for congenital and genetic conditions. Therefore, genetic evaluation, screening, and testing have been offered in the context of PNC for many years in many countries [1, 2]. There have been revolutionary changes in this field in the last 40 years. Having prenatal screening tests significantly reduces the mortality and morbidity rate in mother and baby [3].
Prenatal diagnosis and screening tests are accepted worldwide and applied in Turkey. These tests used: 11-14. nuchal translucency and combined test (double test) by ultrasonography between weeks 16-20, maternal serum AFP, triple and quadruple test between weeks 16-22, 18-22. It is fetal anomaly screening between weeks (Detailed USG). Gestational diabetes screening is performed with a 75-gram Oral Glucose Tolerance Test (OGTT) between weeks 24-28th of pregnancy [4]. When double and triple tests are used together, Down Syndrome can be detected with up to 90% accuracy and less than 5% false positivity [5]. These tests are free for all women in Turkey.
Pregnant women don't need to have these tests in our country. However, many factors affect the decision to have screening tests. First of all, family physicians and obstetricians, the social environment of the pregnant woman, and the media affect the information stage. Pregnant women's educational status and socioeconomic level are also effective in accessing health services and having screening tests [6, 7]. There are different studies in the literature regarding the level of knowledge about prenatal tests [8, 9]. However, studies examining in detail the approach to the trials and the reasons for not having them done are limited.
Our study aims to determine the knowledge level of pregnant women who come to the obstetrics clinic in a university hospital about prenatal screening tests and the factors affecting their decision to have the tests.

Statistical analysis

The collected data were analyzed using SPSS (Statistical Package for Social Sciences) for the Windows Version 25 package program. Normality analysis of numerical data was diagnosed with the Shapiro-Wilk test. Descriptive statistical analyses of the data were first performed. Frequencies for categorical data and measures of central distribution (Mean ± Standard Deviation) for numerical data were calculated. Whether the means of normally distributed numerical data differed significantly between the two independent groups was analyzed with the Independent Samples T-test. The chi-square test was used to compare categorical data. A p-value of less than 0.05 was considered for statistical significance, with a 95% CI.

Materials and Methods

Type of the study

This study is a descriptive cross-sectional study.

Design

The research population comprises approximately 900 pregnant women who are 28 weeks or older and applied to the Sivas Cumhuriyet University Faculty of Medicine, Obstetrics and Gynecology outpatient clinic in the three months starting October 2021. According to the sample calculation, it was aimed to reach at least 209 people at the 90% confidence interval. A research questionnaire was given to 254 of these pregnant women who agreed to participate in the study, and one of the researchers applied to face to face. Data were collected for the survey between October and December 2021. Before the interview, participants were informed about the study, and their informed consent was obtained.

Data collection tool

The data form used in the study consisted of 21 questions. The first 15 questions were about the descriptive features (e.g., age, occupation, education level, living place, income status, habits, history of kinship with the spouse, and chronic diseases) of the pregnant women and their obstetric history (number of pregnancies, gestational week, previous pregnancy situations, pregnancy follow-ups and where they were followed, baby with anomaly history). The last six questions were about prenatal screening tests (e.g., knowledge levels about the prenatal tests, sources of information, cases of having them done, and why they did not have it done).
The researchers prepared questions about the level of knowledge of prenatal screening tests by reviewing the literature. The total knowledge score was calculated by giving 1 point for correct answers and 0 points for incorrect answers. As the score increased, the level of knowledge about the test increased.

Permissions

The Ethics Committee of The Sivas Cumhuriyet University for Noninvasive Clinical Research approved the study (2021/04-52).

Results

Demographic Data and Characteristics of Pregnant Women

Two hundred fifty-four people volunteered to participate in the study. The mean age of the participants was 28.0±5.1 (min:17- max:43). Education levels were 37.0% (n=94) primary education, 34.3%

(n=87) high school, and 28.7% (n=73) higher education. Income levels were 35.0% (n=89) low-income level, 31.1% (n=79) middle-income level, 33.9% (n=86) high-income level. Education levels were 37.0% (n=94) primary education, 34.3% (n=87) high school, and 28.7% (n=73) higher education. Income levels were 35.0% (n=89) low-income level, 31.1% (n=79) middle-income level, 33.9% (n=86) high-income level.

The mean gestational week of the participants was 34.9±3.9 (min:28-max:41). The mean number of pregnancies was 2.4±1.4 (min:1-max:9). The number of living children was 1.1±1.2 (min:0-max:7). None of the pregnant women had a history of children with anomalies. Most of them had regular follow-ups of pregnancy (78.7% regularly, 16.9% partially regularly). 33.9% of the pregnant had follow-ups in the state hospital, 46.5% in the university hospital. Pregnancy-related data are shown in Table 1.

Table 1. Participants' information about pregnancy

N=254	n	%
Pregnancy loss		
Yes	59	23.2
No	195	76.8
Cause of pregnancy loss (N=59)		
Spontaneous abortion	44	74.6
Voluntary termination	2	3.4
Medical termination	6	10.4
Premature-stillbirth	7	11.9
Pregnancy complication		
Yes	29	11.4
No	225	88.6
Abnormal fetal conclusion		
Yes	16	6.3
No	238	93.7
Where was the pregnancy follow-up done?		
Family medicine	9	3.5
Private clinic	41	16.1
Public Hospital	86	33.9
University Hospital	118	46.5
Pregnancy follow-up scheme		
Regular	200	78.7
Partly regular	43	16.9
Irregular	11	4.3
Cigarette		
Smoking	26	10.2
Stopped smoking during pregnancy	29	11.4
Never smoked	199	78.3

Pregnant women most frequently had a detailed ultrasound (80.7%) and double screening test. The rate of those with double and triple screening tests was 51.6%. The frequency of pregnant women who did not have any screening test was 14.2%. The status of pregnant women to have non-invasive prenatal screening tests is shown in Table 2.

Table 2. History of having a noninvasive genetic screening test

	n	%
Double test only	59	23.2
Triple test only	22	8.7
Both the double and triple test	131	51.6
Detailed ultrasonography	205	80.7
Oral Glucose Tolerance Test (OGTT)	93	36.6
No screening test	36	14.2

When asked about the sources of information about screening tests, the most common answer for all screening methods was Obstetrician and Family Physician second. In all prenatal screening tests, those who received notification from the obstetrician had a significantly higher rate of getting the test than those who did not. The status of obtaining information from family physicians and obstetricians of those who had prenatal screening tests is shown in Table 3.

Table 3. The Status of Obtaining Information From The Family Physician or Obstetrician of Those Who Had Prenatal Screening Test

Having the prenatal screening test	Having information from an Obstetrician		p	Having information from FP		p
	Yes	No		Yes	No	
Double test	129 (67.9%)	61 (32.1%)	**<0.001**	49 (25.8%)	141 (74.2%)	0.065
Triple test	108 (70.6%)	45 (29.4%)	**<0.001**	45 (29.4%)	108 (70.6%)	**0.001**
Detailed ultrasonography	142 (69.3%)	63 (30.7%)	**0.003**	66 (32.2%)	139 (67.8%)	**0.001**
OGTT	65 (69.9%)	28 (30.1%)	**<0.001**	36 (38.7%)	57 (61.3%)	0.159

FP: Family Physician, OGTT: Oral Glucose Tolerance Test. Chi-square test was used for analysis

When the participants' knowledge scores about prenatal screening tests are evaluated, respectively, the Detailed ultrasound knowledge score is 5.6±0.9 (min:2-max:7), the Double test knowledge score is 5.0±1.3 (min:2-max:7), OGTT knowledge score is 4, 8±1.1 (min:2) -max: 7) and Triple test knowledge score was 4.7±1.2 (min:2-max:7).

When pregnant women were questioned why they did not have prenatal screening tests, the most common answer for all screening tests was, "I don't think the test is necessary." The second most common reason for not having the dual screening test (32.8%) and detailed ultrasound (30.6%) was because they missed the test. For the OGTT, the second most common reason for not having it done was because they heard from the media that the test was harmful. The reasons for not having a prenatal screening test are shown in Table 5.

Table 5. Reasons for not having a prenatal screening test.

	Double test (not take n=64)	**Triple test (not take n=101)**	**Detailed ultrasonography (not take n=49)**	**OGTT (not take n=161)**
Reason for not taking the test	n (%)	n (%)	n (%)	n (%)
Don't think it's unnecessary	31 (48.4)	67 (66.3)	27 (55.1)	96 (59.6)
Do not hear from the media that it is harmful.	2 (3.1)	1 (0.9)	3 (6,1)	48 (29.8)
Not recommended by my doctor.	5 (7.8)	23 (22.7)	6 (12.2)	24 (14.9)
Don't miss your time	21 (32.8)	14 (13.8)	15 (30.6)	24 (14.9)
Fear of bad outcomes.	4 (6.2)	5 (4.9)	1 (2.0)	10 (6.2)
My spouse/family elders do not allow me to take the test.	0 (0)	1 (0.9)	0 (0)	8 (5.1)
Don't think that the test will harm my baby.	2 (3.1)	2 (1.8)	2 (4.0)	19 (11.8)

Age (p=0.137), education level (p=0.552), place of residence (p=0.285), income level (p=0.410), smoking status (p=0.253), working group (p=0.463), being a consanguineous marriage (p=0.501), presence of chronic disease in the mother (p=0.423), previous pregnancy loss (p=0.492), the institution of follow-up (p=0.330) did not have a significant effect on the fact that the pregnant women had double and triple screening. Having a double test (p=0.005) and triple screening test(p<0.001), regular check-ups(p=0.001), and high double-triple test knowledge scores had a significant effect. Table 6 shows the factors affecting pregnant women's double and triple screening.

Table 6. Factors affecting the double and triple screening of pregnant women

	Had the double and triple test	Not had the double and triple test	p
Regular visits to checkups*	n (%)	n (%)	
Yes	114 (57.0)	86 (43.0)	**0.001**
No	17 (31.5)	37 (68.5)	
Double test knowledge score(M±SD)**	5.2±1.2	4.7±1.4	**0.005**
Triple test knowledge score(M±SD)**	5.1±1.1	4.4±1.3	**<0.001**

Amniocentesis was recommended for 3.5% (n=9) of pregnant women according to prenatal test results. However, none of these pregnant women had undergone amniocentesis. Would you continue the pregnancy if there is any abnormality in your test results? 2.4% (n=6) of the pregnant women said they thought of terminating their pregnancy, and 68.1% (n=173) of them thought of continuing the pregnancy. 29.5% (n=75) answered that they cannot decide on this issue.

Discussion

In our study, we aimed to evaluate the awareness of women who came for pregnancy follow-up in a tertiary hospital about prenatal tests and the factors affecting their decision to have them.

Routine prenatal testing is recommended as a part of prenatal care for all pregnant women in Turkey. Nacar et al. reported that 76.9% of pregnant women had at least one prenatal screening test [7]. In a different study conducted in Turkey, a vast % of pregnant women, 72.5%, approached all screening tests positively [6]. In our study, the rate of pregnant women with any prenatal screening test was 85.8%. It was thought that the fact that most patients (80.4%) had follow-ups at the state hospital or university hospital level affected this issue.

Within the scope of prenatal screening tests, the double test is offered between 11-14 weeks in the current practice. In the study by Seven et al., 36.1% of the pregnant women had either a double or a triple test [8]. In their research, Bilgin et al. found the double and triple difficulties rate as 41% [10]. This rate is similar in different studies in our country [9, 11]. In our study, the rate of those with double and triple tests (51%) was higher than in similar studies. This may be because the research was conducted in a university hospital, and the awareness of Turkish women increased compared to previous years [12].

In our study, the most common test performed by pregnant women was a detailed USG and double screening test. This may be because they are the best-known screening tests. The results are similar to the literature [9,13].

Sociocultural and ethical-moral systems may determine the decision to have prenatal testing. However, providing antenatal counseling has a crucial role in guiding decisions based on the level of knowledge [14].

Therefore, pretest counseling is essential in antenatal care to ensure women understand the limitations and advantages of prenatal testing, whether they want to learn about their fetuses, and what actions to take in the event of an adverse outcome [15]. In our study, the knowledge level of the pregnant women and the counseling from the obstetrician positively affected their having these tests. A different study found that most women received information about prenatal tests, and getting information from an obstetrician most encouraged them to have the trial [16]. This is consistent with our study.

According to the literature, genetic abnormalities and previous miscarriages encourage pregnant women to undergo prenatal testing [8, 16, 17,18]. In our study, age, consanguineous marriage, and last pregnancy loss did not affect the fact that pregnant women had double and triple screening tests. This may be due to the absence of pregnant women with an anomaly in our study.

In Turkey, it is recommended to screen for gestational diabetes between the 24th and 28th weeks of pregnancy [4]. The rate of OGTT in pregnant women in our study was lower than in other tests. When the reasons for not having the difficulty were questioned, the second most common reason was hearing from the media that the test was harmful. Knowledge level about OGTT was also lower than on other tests. Unfortunately, this situation is similar in many studies conducted in Turkey [6, 19, 20]. The uncontrolled statements about diabetes screening during pregnancy in the Turkish media, especially in recent years, affect this situation.

In Islamic beliefs, there are several legitimate reasons for terminating a pregnancy. The most important

reason, and for some Muslim jurists the only reason, is that the mother's health is in danger, and the ongoing pregnancy can even bring about maternal death. We did not question religious beliefs in our research. Turkey is a country with a 98% Muslim population. In our study, amniocentesis was recommended for 3.5% of pregnant women, according to the results of prenatal tests. But none of these pregnant women had undergone amniocentesis. In the case of fetal anomaly, only 2.4% of the women thought of terminating the pregnancy, and most continued the pregnancy. The study conducted by Kutlu et al.[13] determined that the most common reason stated by pregnant women who did not want to have screening tests was "I find it unnecessary because I do not want to terminate my pregnancy." The most common reason why pregnant women did not have all the tests in our study was that they thought they were unnecessary. This may be because they believe the test result will not affect their decision about the continuation of the pregnancy due to their religious beliefs. This situation is similar to the effects of studies on Muslim women's approaches in different countries in the literature [21,23].

Pregnant women and their spouses should be informed about prenatal screening by all health professionals, especially obstetricians and family physicians, and correct counseling should be provided [24]. Although the awareness of pregnant women about prenatal tests is increasing in Turkey, it is still insufficient. It should also be explained that these tests are only screening tests and only identify risks. Pregnant women who are given accurate information and make conscious decisions have a more positive approach to tests [25].

Conclusion

As a result, our study determined that the level of knowledge and the guidance of physicians were very influential in testing. In particular, the media can be used as an effective tool in providing accurate information about OGTT. Most pregnant women thought of continuing their pregnancy even with negative test results. As prenatal genetic screening and testing are optional services, healthcare professionals need to provide women with the necessary education about screening and diagnostic testing to enable them to make informed decisions.

Limitations

Our research was conducted in a single center and a 3rd level hospital. Results cannot be generalized. More qualitative studies are needed to evaluate the reasons for having and not having screening tests. In addition, the researchers created questions measuring the level of knowledge through a literature review, which is not a valid questionnaire.

Declaration of Conflicting Interests

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References

1.Lewis JA (2011) Genetics and genomics impact perinatal nursing. Journal of Perinatal & Neonatal Nursing 25, 144– 147.

2.Skirton H & Barr O (2007) Influences on uptake of Down syndrome antenatal screening: a literature review. Evidence-Based Midwifery 5, 4– 9.

3.Evans MI, Andriole S, Evans SM. Genetics: update on prenatal screening and diagnosis. Obstet Gynecol Clin North Am. 2015 Jun;42(2):193-208. PMID: 26002161.

4.Turkey Public Health Institute (TPHI)), Department of Women and Reproductive Health. (2014). Antenatal Care Guide, Sağlık Bakanlığı Yayın No: 924 Ankara, 2014. Available at: http://bit.ly/1KP4ORI

5.Cunningham FG, Leveno KJ, Bloom SL et al. Prenatal Screening; In William's Obstetrics; 24th ed. New York City: The McGraw Hill Companies; 2014:283-305.

6.Desdicioğlu R, Yıldırım M, Süleymanova İ, Atalay İ, Özcan M, Yavuz AF. Gebe kadınların antenatal testlere yaklaşımını etkileyen faktörler. Ankara Medical Journal, 2017; 17(1).

7.Nacar G. , Ünver H. , Derya Y. A. , Taşhan S. T. Prenatal Tarama Testleri Yaptırmanın Gebelik Anksiyetesine Etkisi. Annals of Health Sciences Research. 2018; 7(2): 35-40.

8.Seven, M., Akyüz, A., Eroglu, K., Daack-Hirsch, S., & Skirton, H. (2017). Women's knowledge and use of prenatal screening tests. Journal of Clinical Nursing, 26(13-14), 1869-1877.

9.Ergün, P. (2011). Gebelerin üçlü tarama testi ve gebelikte yapılan diğer testler hakkındaki bilgi düzeyinin ölçülmesi (Master's thesis, Sağlık Bilimleri Enstitüsü).

10.Bilgin S, Bıldırcın FD, Alper T, Tosun M, Çetinkaya MB, Çelik H, et al. Gebelikte uygulanan tarama testlerinin anne anksiyetesine olan etkisi. Journal of Turkish Society of Obstetrics and Gynecology 2010; 7: 206-11.

11.Sahin, N. H., & Gungor, I. (2008). Congenital anomalies: parents' anxiety, women's concerns before prenatal testing, and women's opinions towards the risk factors. Journal of Clinical Nursing, 17(6), 827-836.

12.Hacettepe University Institute of Population Studies (2014), "2013 Turkey Demographic and Health Survey". Hacettepe University Institute of Population Studies, T.R. Ministry of Development and TÜBİTAK, Ankara,

Turkey. Available at http://,.hips.hacettepe.edu.tr/eng/index.html

13.Kutlu R, Uzun L, Karaoğlu N, Görkemli H. Awareness of Pregnant Women About Routine Applied Screening Tests and Supportive Treatments in a University Hospital. İstanbul Med J 2020; 21(1): 71-7.

14.Menezes M, Meagher S, da Silva Costa F (2013) Ethical considerations when offering non-invasive prenatal testing. Rev Bras Ginecol Obstet 35: 195-198.

15.Chiang HH, Chao YM, Yuh YS (2006) Informed choice of pregnant women in prenatal screening tests for Down's syndrome. J Med Ethics 32.

16.Fumagalli S, Sofia P, Nespoli A, Locatelli A, Colciago E (2017) Variables Affecting the Decision Making to Uptake Prenatal Testing. Insights Reprod Med Vol.1 No.2:9

17.Chan YM, Leung TY, Chan OK, Cheng YK, Sahota DS. Patient's choice between a non-invasive prenatal test and invasive prenatal diagnosis based on test accuracy. Fetal Diagn Ther. 2014;35(3):193-8. Epub 2013 Nov 13. PMID: 24247224.

18.Skutilova V. Knowledge, attitudes and decision-making in Czech women with atypical results of prenatal screening tests for the most common chromosomal and morphological congenital defects in the fetus: selected questionnaire results. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2015 Mar;159(1):156-62. PMID: 23774847.

19.Yaprak M, Gümüştakım RŞ, Tok A, Doğaner A. Gebelerde oral glukoz tolerans testi farkındalığının tespiti. Ankara Medical Journal 2019;3:635-47.

20.Avci DK, Oner E. Examination of the knowledge, attitude and behaviors of pregnant women on screening tests made during pregnancy. East J Med 2018;23(2):84-89.

21.Gitsels-van der Wal JT, Manniën J, Ghaly MM, Verhoeven PS, Hutton EK & Reinders S (2014a) The role of religion in decision-making on antenatal screening of congenital anomalies: a qualitative study amongst Muslim Turkish origin immigrants. Midwifery 30, 297–302.

22.Gitsels-vander Wal JT, Verhoeven PS, Manniën J, Martin L, Reinders S, Spelten E & Hutton EK (2014b) Factors affecting the uptake of prenatal screening tests for congenital anomalies, a multicentre prospective cohort study. BMC Pregnancy and Childbirth 14, 264.

23.Gitsels-vander Wal JT, Martin L, Manniën J, Verhoeven P, Hutton EK & Reinders S (2015) Antenatal counseling for congenital anomaly tests: Pregnant Muslim Moroccan women's preferences. Midwifery 31, 50– 57.

24.NICE (2021) Antenatal care for uncomplicated pregnancies. Clinical Guidelines, p: 132.

25.Rowe HJ, Fisher JR & Quinlivan JA (2006) Are pregnant Australian women well informed about prenatal genetic screening? A systematic investigation using the Multidimensional Measure of Informed Choice. Australian and New Zealand Journal of Obstetrics and Gynaecology 46(5): 433-439.

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Type 2 Diabetes Mellitus Screening: The Sample of Sivas

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Research Article

History

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ABSTRACT

The aim of the study is to screen for Type 2 Diabetes Mellitus (DM), to determine the risk of DM and to evaluate the factors affecting it. It is a descriptive study. The population of the research consisted of people over the age of 18 living in Sivas who were not diagnosed with diabetes. The sample of the research consisted of individuals over the age of 18 who did not have diabetes and participated in the event, which was organized as part of the 14 November 2022 "World Diabetes Day" event, which continued between 08.00-17.00. In order to reach the universe, a stand was set up in the city center in the square where the people are concentrated. Capillary blood glucose measurement, a questionnaire including height, weight, demographic characteristics and Finnish Diabetes Risk Questionnaire (FINDRISK) were applied to the patients. FINDRISK consists of 8 questions. It determines an individual's risk of developing diabetes in the next ten years. Results are shown as frequencies, mean±standard deviation. Pearson correlation analysis, Student-T test and One way ANOVA test were applied. P<0.05 was considered significant at the 95% confidence interval.78.2% (n=560) of 716 participants were male and 21.8% (n=156) were female. 74.2%(n=531) of them were married. 39.5% (n=283) of them were primary school graduates. 30.2%(n=216) of them were working in any job. 30.9% (n=221) were smokers. 42.5% (n=304) had a chronic disease other than DM. Age groups; 25.8%(n=185) were under 45 years old, 17.7%(n=127) were 45-54 years old, 28.9%(n=207) were 55-64 years old, 27.5% (n=n= 197) of them were over 64 years old. The mean body mass index (BMI) of 684 people who accepted the height-weight measurement was 27.5±4.5. Capillary blood glucose mean of the participants was 130.9±57.0 (min:51-max:494). The mean FINDRISK score was 11.1 ± 5.68 (min:0-max:26). Participants' FINDRISK scores; 20.9% (143) were found to be high and 6.7% (46) were found to be very high. A weakly significant positive correlation was found between FINDRISK score and capillary blood glucose levels (p<0.001; r=0.244). A significant difference was found between the diabetes risk status of the participants and their marital status, education status, employment status, and presence of chronic disease (respectively; p<0.001; 0.004; 0.001; <0.001). The rate of diabetes was higher in married people than in single people, those who did not work than those who worked, and those who had additional chronic diseases than those without. FINDRISK scores were found to be higher than different studies in the literature in the study conducted with population screening. Early identification of groups at high risk of diabetes will reduce the disease and burden of diabetes. At this stage, it will be advantageous to use easy-to-apply and inexpensive scanning methods such as FINDRISK.

Keywords: Diabetes mellitus, screening, FINDRISK, diabetes risk, score

Tip 2 Diyabetes Mellitus Taraması: Sivas Örneği

Süreç

Geliş: 07/07/2022
Kabul: 22/09/2023

ÖZ

Çalışmanın amacı Tip 2 Diyabetes Mellitus (DM) taraması yapmak, DM riskini belirlemek ve etkileyen faktörleri değerlendirmektir. Bu çalışma tanımlayıcı bir çalışmadır. Araştırmanın evreni, Sivas'ta yaşayan 18 yaş üstü, diyabet tanısı konmamış kişilerden oluşturulmuştur. Araştırmanın örneklemini 14 Kasım 2022 "Dünya Diyabet Günü" etkinliği kapsamında düzenlenen ve 08.00-17.00 saatleri arasında devam eden etkinliğe katılan 18 yaş üstü, diyabet hastası olmayan bireyler oluşturmaktadır. Evrene ulaşmak için şehir merkezinde insanların yoğunlaştığı meydanda bir stant kuruldu. Hastalara kılcal kan şekeri ölçümü, boy, kilo, demografik özelliklerin yer aldığı anket ve Finlandiya Diyabet Risk Anketi (FINDRISK) uygulandı. FINDRISK 8 sorudan oluşmaktadır. Bir kişinin önümüzdeki on yıl içinde diyabet geliştirme riskini belirlemektedir. Sonuçlar sıklık, ortalama±standart sapma olarak gösterilmiştir. Pearson korelasyon analizi, Student-T testi ve One way ANOVA testi uygulandı. P<0.05, %95 güven aralığında anlamlı kabul edildi. 716 katılımcının %78,2'si (n=560) erkek, %21,8'i (n=156) kadındı. Bunların %74,2'si (n=531) evlidir. Bunların %39,5'i (n=283) ilkokul mezunuydu. %30,2'si (n=216) herhangi bir işte çalışıyordu. %30,9'u (n=221) sigara içiyordu. %42,5'inin (n=304) DM dışında kronik bir hastalığı vardı. Yaş grupları; %25,8'i (n=185) 45 yaş altı, %17,7'si (n=127) 45-54 yaş arası, %28,9'u (n=207) 55-64 yaş arası, %27,5'i (n=n= 197) bunlardan 64 yaşın üzerindeydi. Boy-kilo ölçümünü kabul eden 684 kişinin ortalama vücut kitle indeksi (BMI) 27,5±4,5 olarak belirlendi. Katılımcıların kapiller kan şekeri ortalaması 130,9±57,0 (min:51-maks:494) idi. Ortalama FINDRISK skoru 11,1±5,68 (min:0-maks:26) idi. Katılımcıların FINDRİSK puanları; %20,9'u (143) yüksek, %6,7'si (46) çok yüksek olarak bulunmuştur. FINDRISK skoru ile kapiller kan şekeri düzeyleri arasında pozitif yönde zayıf düzeyde anlamlı bir korelasyon bulundu (p<0,001; r=0,244). Katılımcıların diyabet risk durumları ile medeni durumları, eğitim durumları, çalışma durumları ve kronik hastalık varlığı arasında anlamlı farklılık bulunmuştur (sırasıyla; p<0,001; 0,004; 0,001; <0,001). Evlilerde diyabet görülme oranı bekarlara göre, çalışmayanlarda çalışanlara göre, ek kronik hastalığı olanlarda çalışmayanlara göre daha yüksekti.

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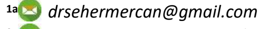
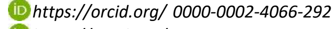
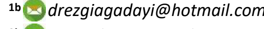
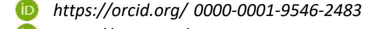
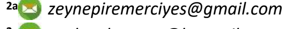
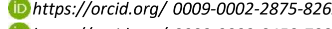
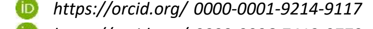
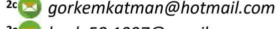
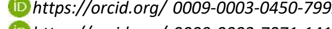
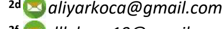
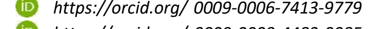
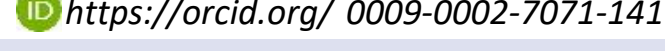
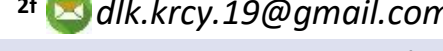
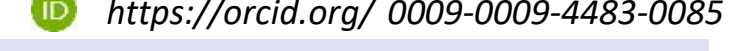
Toplum taramasıyla yapılan çalışmada FINDRISK puanlarının literatürdeki farklı çalışmalara göre daha yüksek olduğu görüldü. Diyabet riski yüksek olan grupların erken belirlenmesi diyabet hastalığını ve yükünü azaltacaktır. Bu aşamada FINDRISK gibi uygulaması kolay ve ucuz tarama yöntemlerinin kullanılması avantajlı olacaktır.

Anahtar sözcükler: Diyabetes Mellitus, tarama, FINDRISK, diyabet riski, puan

[1a]  *drsehermercan@gmail.com*  *https://orcid.org/ 0000-0002-4066-292* [1b]  *drezgiagadayi@hotmail.com*  *https://orcid.org/ 0000-0001-9546-2483*
[2a]  *zeynepiremerciyes@gmail.com*  *https://orcid.org/ 0009-0002-2875-8262* [2b] *mmertkoc1@gmail.com*  *https://orcid.org/ 0000-0001-9214-9117*
[2c]  *gorkemkatman@hotmail.com*  *https://orcid.org/ 0009-0003-0450-7992* [2d]  *aliyarkoca@gmail.com*  *https://orcid.org/ 0009-0006-7413-9779*
[2e] *husk.58.1997@gmail.com*  *https://orcid.org/ 0009-0002-7071-1417* [2f]  *dlk.krcy.19@gmail.com*  *https://orcid.org/ 0009-0009-4483-0085*

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Introduction

Diabetes is a serious chronic disease that occurs as a result of insufficient insulin production or inability to use the produced insulin in the body, resulting in a long-term metabolic disorder. Diabetes affects an estimated 537 million adults aged 20 to 79 worldwide. By 2030, 643 million people worldwide will have diabetes, and by 2045 this number will rise to 783 million [1]. The main reasons for this are the increase in obesity and physical inactivity due to population growth, aging and lifestyle changes brought about by urbanization [2]. The International Diabetes Federation (IDF-2021) reports that 10.5% of the adult population (20-79 years old) has diabetes, and almost half of them are not aware that they live with this condition [3].

According to the TURDEP-II study data, 42% of the adult population in our country is diabetic or prediabetic [4].Similar to world data, awareness of diabetes is low in our country. It is known that the majority of diabetics are not aware of the disease, and this issue emerges as an important problem [5]. In our country, this rate was expressed as 32%. Due to the low awareness of diabetes, individuals who have not yet been diagnosed with diabetes but have a high risk of diabetes should be identified. In this process, "risk screening" is of great importance in determining diabetes risk factors and catching diabetes at an early stage. Although the benefits and financial burden of community-based diabetes screening are discussed, it is emphasized that screening activities are important for raising public awareness [2].

One of the risk questionnaires (eg FINDRISK, ADA risk questionnaire) developed to identify individuals at high risk for diabetes and prediabetes easily and cost-effectively can be used [4]. Our aim in this study is to screen for Type 2 Diabetes Mellitus (DM) in the population and to determine the risk of developing DM within 10 years and to evaluate the factors affecting this situation.

Material Method

Study type

This study is a descriptive cross-sectional study.

Design:

The population of the research consisted of 390,318 people living in the center of Sivas. When the population is calculated in the 95% confidence interval according to the known sample calculation, the number of people to be reached was calculated as 384 people. In order to reach the universe in the research, a stand was set up in the city center in the square where the people are concentrated. The sample of the research consisted of individuals over the age of 18 who did not have diabetes and participated in the event, which was organized as part of the 14 November 2022 “World Diabetes Day” event, which continued between 08.00-17.00.

Data collection tool:

The sociodemographic questionnaire form prepared by the researchers was filled in by face-to-face interview method after giving general information about diabetes to the participants. The age, gender, marital status, education level, occupation, smoking habits and exercise status of the individuals were recorded in this questionnaire. The Finnish Type 2 Diabetes Risk Assessment Questionnaire (FINDRISK) was used. FINDRISK; It consists of eight questions. It was developed by the Finnish Diabetes Association in 2003 as part of the Finnish Type 2 Diabetes Prevention Programme. FINDRISK can be easily used for this purpose in daily practice [6]. It has been translated into Turkish by the Turkish Society of Endocrinology and Metabolism (TEMD) and is recommended for diabetes screening in our country [5]. This test determines a person's risk of developing diabetes in the next ten years, thus identifying people with high risk levels. FINDRISK is a simple, easy and straightforward test. The weight of each question in the test is different. In FINDRISK, age, body mass index, waist circumference (evaluated differently in women and men), exercise status, frequency of consumption of vegetables and fruits, history of antihypertensive treatment,

history of hyperglycemia, and family history of diabetes are evaluated. The maximum possible score is 26. A score of 15 and above increases the risk. It is recommended that these individuals be screened for diabetes with advanced laboratory methods [7].

After the questions were answered by the participants, the height, weight, waist circumference and blood glucose measurements of the individuals who accepted were made. Random capillary blood glucose measurement was performed during screening. Capillary whole blood sample was taken at any time of the day, without questioning the hunger status, with the same brand and model glucometer with international quality certificate. Plasma glucose was calculated from capillary blood according to the formula “Plasma glucose (mg/dl) = 0.102 + [19.295 x capillary blood glucose (mg/dl)/18]”. In the scans, the cut-off value was accepted as 140 mg/dl. Those who got 12 points and above according to the FINDRISK score and those with random blood glucose ≥140 mg/dl regardless of the risk score were referred to a health institution for further examinations.

Statistical methods used:

The collected data were analyzed using SPSS (Statistical Package for Social Sciences) for Windows Version 25 package program. Normality analysis of numerical data was analyzed with the Shapiro-Wilk test. Descriptive statistical analyses of the data were first performed. Frequencies for categorical data and measures of central distribution (Mean ± Standard Deviation) for numerical data were calculated. Independent Samples test whether the means of normally distributed numerical data differ significantly between two independent groups; One way ANOVA test was used to analyze whether there was a significant difference between more than two independent groups. Post-hoc analysis of homogeneous variances was analyzed by Bonferroni test. Pearson correlation analysis was applied. Chi-square test was used to compare categorical data. P<0.05 was considered significant at 95% confidence interval.

Permissions:

Ethics committee approval for the study was obtained from Sivas Cumhuriyet University Clinical Research Ethics Committee (Approval date/number: 2022-06/05).

Results

Demographic data characteristics of the participants

78.2% (n=560) of 716 people participating in the study were male and 21.8% (n=156) were female. 74.2% (n=531) were married, 25.8 % (n=185) were single. Education levels 4.3 % (n=31) were illiterate, 39.5 % (n=283) primary school, 11.0 % (n=79) secondary school, 26.4 % (n=189) high school, 18.7% (n=) 134) was a university graduate. business situations; 30.2% (n=216) were working, 38.8% (n=278) were retired, 28.5% (n=204) were unemployed, and 2.5% (n=18) were students. 30.9% (n=221) were smokers. 42.5% (n=304) had a chronic disease other than DM. Age groups; 25.8 % (n=185) were under 45 years old, 17.7% (n=127) were 45-54 years old, 28.9% (n=207) were 55-64 years old, 27.5% (n= 197) of them were over 64 years old. Body mass index (BMI) values of 684 people who accepted the height-weight measurement; 1.8% (n=12) were underweight, 29.1% (n=199) were normal, 40.8% (n=279) were overweight, 22.8% (n=156) were mildly obese, 5.0% (n=34) were moderately obese 0.6% (n=4) were morbidly obese. The mean BMI of the participants was 27.5±4.5. The mean BMI of men was 27.3±4.5, while that of women was 27.9±5.5 (p=0.147).

The calculated plasma glucose mean of the participants was 139.5±60.8 (min:54-max:494). 12.1% (n=83) were 200 mg/dl and above. 87.9% (n=601 were 200 mg/dl and below. Mean capillary blood glucose was 130.9±57.0 (min:51-max:494). Medication use for high blood pressure in 69.7% of the participants (n=477). Diabetes was diagnosed in any family member in 44.2% (n=302). FINDRISK questionnaire data of the participants are shown in Table 1.

Table 1. Participants' FINDRISK survey data		
	n	%
Age		
<45 years	167	24.4
45-54 years	126	18.4
55-64	200	29.2
>64	191	27.9
BMI		
<25 kg/m2	214	31.3
25-30 kg/m2	276	40.4
>30 kg/m2	194	28.4
Waist circumference measurement		
Female<80 cm / Male<94 cm	151	22.1
Female 80-88 cm / Male 94-102 cm	156	22.8
Female >88 cm / Male >102 cm	377	55.1
How often do you consume vegetables and fruits?		
Every day	444	64.9
Not everyday	240	35.1
Do you mostly exercise at least 30 minutes a day?		
Yes	496	72.5
No	187	27.5
Have you ever used medication for high blood pressure or have you ever had high blood pressure?		
Yes	477	69.7
No	207	30.3
Have you been told by the doctor that your blood sugar is high or borderline?		
Yes	488	71.3
No	196	28.7
Has any of your family members been diagnosed with diabetes?		
No	382	55.8
Yes, uncle, aunt, uncle, cousin or niece (Secondary nearby)	71	10.4
Yes, biological father, mother, sibling or child (First degree relative)	231	33.8

The mean FINDRISK score of the participants was 11.1 ± 5.68 (min:0-max:26). Participants' FINDRISK scores; 23% (157) were low, 32% (219) mild, 17.4% (119) moderate, 20.9% (143) high, and 6.7% (46) very high.

A weakly significant positive correlation was found between FINDRISK score and capillary blood glucose levels ($p<0.001$; $r=0.244$). FINDRISK average score; married, non-diabetic chronic disease, calculated Plasma glucose≥200 mg/dl was significantly higher. Comparison of FINDRISK results with various factors is shown in Table 2.

Table 2. **Comparison of FINDRISK results with various factors**

	FINDRISK score mean	p
Total	11.1±5.6	-
Gender		
Female	12.3±6.3	0.070
Male	11.3±5.2	
Educational Status		
İlliterate	11.1±6.6	**0.003***
Primary school	11.7±5.5	
Middle school	10.6±5.1	
High school	11.6±6.1	
University	9.5±5.1	
Marital status		
Married	11.8±5.4	**<0.001**
Single	9.0±5.9	
Smoking		
Yes	9.9±5.6	**<0.001**
No	11.6±5.6	
Non-Diabetes Chronic Disease		
Present	13.8±5.5	**<0.001**
Absent	9.1±4.8	
Calculated PG		
≥200 mg/dl	15.0±4.9	**<0.001**
<200 mg/dl	11.0±5.4	

PG, plasma glucose; DM, diabetes mellitus
*One way ANOVA test, Bonferoni Post Hoc analysis; Significant difference was found between university and primary school, university and high school.

A significant difference was found between the diabetes risk status of the participants and their marital status, education status, employment status, and presence of chronic disease (respectively; $p<0.001$; 0.004; 0.001; <0.001). High and very high risk rate was more common in married (31.6%) than single (16.1%). 16% of those with university or higher education were in the high and very high risk group. This rate is lower than other education categories. The diabetes risk of unemployed (31%) was significantly higher than that of working (19.7%). Those with additional chronic diseases other than diabetes (46.3%) had a higher and very high risk compared to those without (14.1%) (Table 3).

***Table 3*. Sociodemographic characteristics of the participants by diabetes risk status**

Sociodemographic characteristics	Low and mild risk		Moderate risk		High and very high risk		
	n	%	n	%	n	%	p
Gender							
Female	72	49.7	24	16.6	49	33.8	0,170
Male	304	56.4	95	17.6	140	26	
Marital status							
Married	257	50.4	92	18	161	31.6	**<0.001**
Single	119	68.4	27	15.5	28	16.1	
Educational status							
Primary education	205	54.2	97	17.7	106	28	**0,004**
High school	90	51.4	23	13.1	62	35.4	
University and above	81	61.8	29	22.1	21	16	
Working status							
Worker	115	56.7	48	23.6	40	19.7	**0.001**
Inoperative	261	54.3	30	15.4	149	31	
Smoking							
Yes	127	60.2	35	16.6	49	23.2	0,152
No	249	52.6	84	17.8	140	29.6	
Non-Diabetes Chronic Disease							
Present	101	35.2	53	18.5	133	46.3	**<0.001**
Absent	275	69.3	66	16.6	56	14.1	

Discussion

DM is a chronic disease with an increasing incidence. It has become one of the most important public health problems with the increase in life expectancy and obesity in the world and in our country [8]. However, unfortunately, awareness of diabetes is low in our society. We carried out a diabetes screening in Sivas to raise awareness within the scope of World Diabetes Day. The findings were discussed by comparing them with the data in the literature.

Although there are different methods to identify people at high risk of diabetes, there is no established practice in routine practice yet. In this study, participants' diabetes risk levels and related factors were evaluated using FINDRISK, and high-risk individuals were referred for a definitive diagnosis. In our research, 23% of the participants were found to be low risk, 32% mild, 17.4% moderate, 20.9% high, and 6.7% very high risk. In the population-based study conducted by Çevik et al., 37.5% of the participants had an increased risk (high, very high risk) [9]. In the study of Kutlu et al., the increased risk was found to be 15.5% [10]. Our results were similar to the literature.

In the study of Coşansu et al., the FINDRISK mean score of the participants was 7.46 [11]. In different studies, similar results were obtained with average scores [12,13]. In a study conducted in Greece using FINDRISK, the mean risk score was found to be 13.1±4.9 (14). The mean FINDRISK score of our study was 11.1±5.68. Similar to the study of Makrilakis et al., 57.1% of the participants in our study were 55 years or older [14]. The difference between the high-risk scores may be due to the high average age of the participants.

Our study's mean FINDRISK score was 12.3±6.3 for women and 11.3±5.2 for men. In different studies in the literature, women had a higher risk score, similar to our study [10,11,15].

In our study, there was a significant positive correlation between FINDRISK score and capillary blood glucose levels. FINDRISK average score; married, non-diabetic chronic disease, calculated PG ≥200 mg/dl was significantly higher. This

situation was similar in different studies in the literature [10,16].

When the relationship between diabetes risk and smoking habit was examined, no significant relationship was found. Similar to our results, different studies conducted in Turkey did not find a significant relationship between smoking and FINDRISK score [10,17].

In their study, Väätäinen et al. found a significantly higher risk of diabetes in individuals who did not work, similar to our findings [16]. This may be due to the high average age of the unemployed population and the lack of physical activity.

Studies have shown that the prevalence of hypertension is 2 times higher in those with a high risk of diabetes compared to those with a low risk [18]. Many studies have also found that systolic and diastolic blood pressure are positively correlated with diabetes risk [10,19,20]. In our study, the calculated PG mean of the participants was 139.5±60.8. This value was higher than other similar studies. Consistent with the literature, this may be supported by the fact that the majority of the participants had a history of high blood pressure.

Obesity is one of the most important risk factors for diabetes. In different studies in the literature, as body mass index increases, diabetes risk and incidence also increase [20,21]. In our study, 30% were of normal weight, while the remainder were overweight or obese. The participants' calculated plasma glucose mean and FINDRISK mean score were higher than in other population-based studies. We think that this may be due to the fact that the majority of the participants in our study had a body mass index above the average.

Our most important limitation is the inability to generalize the results, since our research was conducted in a single city and in one day.

In conclusion, diabetes is a chronic disease that is increasing in prevalence in our country and in the world and can cause many different complications. Early identification of people at high risk of diabetes is extremely important to combat diabetes and its consequences. In this regard, health professionals need to conduct community-based studies with broad participation. The most important limitation of our research is that it was conducted in a single province. Especially primary care plays an important role in increasing the awareness of diabetes in society and minimizing diabetes risk factors. Early identification of risky groups and immediate intervention will reduce the disease burden and financial burden of diabetes. At this stage, using easy-to-apply and inexpensive scanning methods such as FINDRISK will be advantageous.

References

1. Kumar A, Gangwar R, Ahmad Zargar A, Kumar R, Sharma A. Prevalence of diabetes in India: A review of IDF Diabetes Atlas 10th edition. Current Diabetes Reviews. 2023 Apr. DOI: 10.2174/157339981966623041309420 0. PMID: 37069712.
2. T.C. Sağlık Bakanlığı. Türkiye Diyabet Önleme ve Kontrol Programı Eylem Planı (2011-2014). Ankara: Anıl Matbaası, 2011
3. International Diabetes Federation (IDF 2021). Diabetes Atlas) 9th ed. Erişim Tarihi:10.07.202. https://idf.org/e-library/ epidemiology-research/diabetes-atlas/159-idfdiabetes-atlas-ninth-edition-2021.htm
4. Türkiye endokrinoloji ve metabolizma derneği (TEMD) diabetes mellitus ve komplikasyonlarının tanı, tedavi ve izlem kılavuzu-2022. Erişim Tarihi: 10.07.2023 http://temd.org.tr/admin/ uploads/tbl_kilavuz/20200625154506-2020tbl_ kilavuz86bf012d90.pdf7syf 15.
5. Satman, I., Omer, B., Tutuncu, Y., Kalaca, S., Gedik, S., & Dinccag N, et al.(2013). Twelveyear trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol. 28 (2): 169–180.
6. Finnish Diabetes Association, Programme for the Prevention of Type 2 Diabetes in Finland 2003.2010.http://www.diabetes.fi/files/1108/Programme_for_the_Prevention_of_Type_2_Diabetes_in_Finland_2003-2010.pdf. Erişim tarihi: 15.10.2014.
7. Lindström J, Tuomilehto J. A practical tool to predict type 2 diabetes risk. Diabetes Care 2003;26(3):725-31
8. Kulak E, Berber B, Temel H, ve ark. Aile hekimliğine başvuran bireylerde tip 2 diyabet risk düzeyinin belirlenmesi. Türk Aile Hek Derg 2019; 23 (1): 20-30
9. Çevik AB, Karaaslan MM, Koçan S, et al. Prevalence and screening for risk factors of type 2 diabetes in Rize, Nourtheast Turkey: findings from a

population-based study. Prim Care Diabetes 2016;10(1):10-8.

10. Kutlu R, Sayın S, Koçak A. Tanı Almamış Tip 2 Diyabet İçin Bir Tarama Metodu Olarak Fin Diyabet Risk Anketi (FINDRISK) Uygulanabilir mi? Konuralp Tıp Dergisi 2016;8(3):158-66.
11. Cosansu G, Celik S, Özcan S, Olgun N, Yıldırım N, Demir HG. Determining type 2 diabetes risk factors for the adults: A community based study from Turkey. Prim Care Diabetes 2018;12(5):409-15.
12. Zhang L, Zhang Z, Zhang Y, Hu G, Chen L. Evaluation of Finnish Diabetes Risk Score in screening undiagnosed diabetes and prediabetes among U.S. adults by gender and race: NHANES 1999- 2010. PLoS One 2014;9(5):e97865.
13. Awad A, Alsaleh FM. 10-year risk estimation for type 2 diabetes mellitus and coronary heart disease in Kuwait: a cross-sectional population-based study. PLoS One 2015;10(1):e0116742.
14. Makrilakis K, Liatis S, Grammatikou S, et al. Validation of the Finnish diabetes risk score (FINDRISC) questionnaire for screening for undiagnosed type 2 diabetes, dysglycaemia and the metabolic syndrome in Greece. Diabetes Metab 2011;37(2):144
15. Janghorbani M, Adineh H, Amini M. Finnish Diabetes Risk Score to predict type 2 diabetes in the Isfahan diabetes prevention study. Diabetes Res Clin Pract.2013;102(3):202-9.
16. Väätäinen S, Cederberg H, Roine R, et al. Does Future Diabetes Risk Impair Current Quality of Life? A Cross-Sectional Study of Health-Related Quality of Life in Relation to the Finnish Diabetes Risk Score (FINDRISC). PLoSOne.2016;11(2):e0147898.
17. Cevik Akyil R, Miloglu O, Olgun N et al.A comparison of three different diabetes screening methods among dental patientsin Turkey. Pak J Med Sci.2014;30(1):65-9.
18. Önder MR, ÖzerkanF. Diyabet ve Hipertansiyon. Türkiye KlinikleriJ Cardiol 2000;13(5):401-3
19. Tankova T, Chakarova N, Atanassova I et al. Evaluation of the Finnish Diabetes Risk Score as a screening tool for impaired fasting glucose, impaired glucosetolerance and undetected diabetes. Diabetes Res Clin Pract. 2011;92(1):46-52.
20. Costa B, Barrio F, Piñol JL, et al. Shifting from glucose diagnosis to the new HbA1c diagnosis reduces the capability ofthe Finnish Diabetes Risk Score (FINDRISC) to screen for glucose abnormalities with in a real life primary healthcare preventive strategy. BMC Med.2013;11:45
21. Saaristo T, Peltonen M, Lindström J, et al. Cross-sectional evaluation of the Finnish Diabetes Risk Score: a tool to identify undetected type 2 diabetes, abnormal glucose tolerance and metabolic syndrome. Diab Vasc Dis Res 2005;2:67-72.

Cumhuriyet Medical Journal, 45(3): 36-43 2023
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Determination of Industry 4.0 Conceptual Awareness Levels of Midwifery Students

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Research Article

History

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ABSTRACT

Along with technological innovations in the world, the health industry has also developed and entered the digital transformation process. This study was designed as a descriptive study aiming to determine the awareness of midwifery students on Industry 4.0.

The population of the study consisted of students of the midwifery department of a university. The minimum sample size was calculated in G*power 3.1.9 program. Accordingly, the number of samples to be included in the study for 95% statistical power 0.05 margin of error was determined as 210. The study was completed with 257 midwifery students, taking possible losses into account. Personal Information Form and Industry 4.0 Conceptual Awareness Scale were used as data collection tools.

The average age of the students in the study was 21.22 ± 1.84 years, 31.9% of the students were 2nd-year students in the Department of Midwifery, 52.9% of the students had their own computers, 100% of them used smartphones, and 60.7% used computers. The average score of the students on the scale was 89.98 ± 30.5, and it was determined that the students' Industry 4.0 Conceptual Awareness was at a medium level according to the score obtained from the scale. When the relationship between the place where the students stayed and the scores obtained from the scale was examined, it was determined that there was a significant difference between the scores obtained from the scale of the students staying in the state dormitory and the students staying in the private dormitory ($p < 0.05$).

In the study, it was determined that the midwifery department students' Industry 4.0 Conceptual Awareness levels were at a moderate level, and the place of residence positively affected the level of awareness of this concept.

Keywords: Digital Technology, Midwifery, Industry, Awareness, Health

Ebelik Bölümü Öğrencilerinin Endüstri 4.0 Kavramsal Farkındalık Düzeylerinin Belirlenmesi

Süreç

Geliş: 08/04/2023
Kabul: 25/09/2023

ÖZ

Dünyada teknolojik yeniliklerle birlikte sağlık endüstrisi de gelişim göstermiş ve dijital dönüşüm sürecine girilmiştir**.** Bu araştırma ebelik bölümü öğrencilerinin endüstri 4.0 farkındalıklarını belirlemeyi amaçlayan tanımlayıcı nitelikte tasarlanmıştır.

Araştırmanın evrenini bir üniversitenin ebelik bölümü öğrencileri oluşturmaktadır. Minimum örneklem sayısı G*power 3.1.9 programında hesaplanmıştır. Buna göre %95 istatistiksel güç 0.05 hata payı için araştırmaya dahil edilmesi gereken örneklem sayısı 210 olarak belirlenmiştir. Araştırmada olası kayıplarda göz önünde bulundurularak 257 ebelik öğrencisi ile tamamlanmıştır. Araştırmada veri toplama aracı olarak Kişisel Bilgi Formu ve Endüstri 4.0 Kavramsal Farkındalık Ölçeği kullanılmıştır.

Araştırmada öğrencilerin yaş ortalaması 21.22±1.84 yıl olup, öğrencilerin %31.9'u Ebelik bölümü 2.sınıf öğrencisidir. %52.9'unun kendine ait bilgisayarı olup, %100'ü akıllı telefon, %60.7'si bilgisayar kullanmaktadır. Öğrencilerin ölçekten aldığı puan ortalaması 89.98 ± 30.5 olup, ölçekten alınan puana göre öğrencilerin Endüstri 4.0 Kavramsal Farkındalıklarının orta düzeyde olduğu belirlenmiştir. Öğrencilerin kaldığı yer ve ölçekten alınan puanlar arasındaki ilişki incelendiğinde devlet yurdunda kalan öğrenciler ile özel yurtta kalan öğrencilerin ölçekten alınan puanlar arasında anlamlı fark olduğu belirlenmiştir ($p< 0.05$).

Araştırmada ebelik bölümü öğrencilerin Endüstri 4.0 Kavramsal Farkındalık Düzeylerinin orta derecede olduğu ve yaşanılan yerin bu kavrama ilişkin farkındalık düzeyini olumlu yönde etkilediği belirlenmiştir.

Anahtar sözcükler: Dijital Teknoloji**,** Ebelik, Endüstri, Farkındalık, Sağlık

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Introduction

Automation and digitalization in production systems have rapidly developed computer technologies. With this development, Industry 4.0 has taken its place in our lives by focusing on technology with the spread of production robots and internet infrastructure [1-3]. This concept is a revolution based on the adoption of information technology-based production method and applications [4]. The health industry has also developed with technological innovations in the world. Today, the need for health services has increased with the increase in the average life expectancy. Along with this need, problems such as increasing population, epidemics, pandemics, and limited resources force the health system. The health system should fulfill its function in the best way by eliminating or minimizing these problems. In this process, the digital transformation process in health has been entered by leaving traditional methods aside, keeping up with the developing technology, and producing solutions to problems with the help of technology [5, 6]. In particular, the recent COVID-19 pandemic has led to a significant loss of human life worldwide and has greatly affected healthcare services. Industry 4.0 technologies have created effective supply chain management to meet customized demands in healthcare [7]. Industry 4.0 has the potential to meet customized requirements during COVID-19-related emergency crises, and an Industry 4.0-based approach was successfully utilized during the COVID-19 pandemic [8, 9]. Furthermore, the Internet of Things, artificial intelligence, big data analytics, and 3D printing have been used extensively to combat the COVID-19 pandemic [7].

The global health sector continues to grow rapidly, and Industry 4.0 is one of the fastest-growing sectors [10]. These developments in Industry 4.0 have positively affected Health 4.0, and digital transformation has also taken place in health. With Health 4.0, people's life expectancy has been extended with improvements in the treatment and diagnosis of diseases 11. In addition, a vision of a personalized, patient-centered approach, preventive, sensitive, widespread, and participatory healthcare services has emerged [11, 12]. In the hospitals of the future, an efficient process will be measured not by the number of beds but by the correct use of technology. Hospitals will create their own future by developing technological digital investments [12]. Now, thanks to the digital transformations brought by Industry 4.0, new concepts have started to emerge in Health 4.0. Examples of these concepts include 5G, cloud, robotics, artificial intelligence, the Internet of Things, quantum computers, virtual reality, and big data 5.

Industry 4.0 is now widely used in the field of healthcare and education [13, 14]. As a result of a study, it was observed that the virtual reality simulation developed had positive effects on students' newborn care skills satisfaction levels and increased their sense of self-confidence [15]. In a study conducted on health education, A virtual field experience training program accompanied by simulation was implemented for midwifery department students who could not complete clinical practice during the pandemic period. With the application, an education model that will contribute to the provision of reliable and sustainable health services has been developed [16]. In a study, a model with an Artificial Neural Network (ANN) algorithm was used to identify problems that may occur during pregnancy at an early stage through remote pregnancy monitoring. With this model, some parameters were scored according to the determined criteria to describe the symptoms during pregnancy. These criteria include last menstrual date, nausea-vomiting, craving, appetite, body mass index, breast tenderness, urination-defecation pattern, pulse, blood pressure, body temperature, vaginal bleeding, and psychosocial status. In the study examining the effectiveness of the model, the medical records of 172 people were examined. According to the results of the study, the ANN-based model can be used to identify problems during pregnancy with an accuracy of around 78% [17]. As seen in these studies in the literature, midwives in many parts of the healthcare field also need to have knowledge about Industry 4.0 and its developmental process. In addition, it is necessary to determine the awareness level of midwives to keep up with this process. Thus, this study was conducted to determine the awareness of student midwives about Industry 4.0.

Research Questions

1.What is the level of Industry 4.0 awareness of midwifery students?

2.Is there a difference between the sociodemographic characteristics of midwifery students and their Industry 4.0 Awareness Levels?

Material Method

Population and Sample of the Research

The population of the study consisted of N=368 students enrolled in Tokat Gaziosmanpaşa University, Faculty of Health Sciences, Department of Midwifery. The minimum sample size was calculated in G*power 3.1.9 program. Accordingly, the number of samples that should be included in

the study for 95% statistical power 0.05 margin of error was calculated as 210. The study was completed with 257 midwifery students, taking into account possible losses.

Inclusion criteria: Between the dates of the study, students enrolled in Tokat Gaziosmanpaşa University, Faculty of Health Sciences, Department of Midwifery, continuing formal education and volunteering to participate in the study were included.

Dependent variables: Scores from the Industry 4.0 Awareness Scale

Independent variables: Socio-demographic characteristics of students

Data Collection

The implementation of the study was carried out between May 16, 2022, and June 20, 2022. The questionnaires were uploaded to https://docs.google.com/forms/, and the link address was delivered online via WhatsApp to the students of Tokat Gaziosmanpaşa University Faculty of Health Sciences, Department of Midwifery. An informed consent page was presented on the introduction page of the questionnaire, and the students who accepted continued the survey.

Data Collection Tools

"Socio-demographic Information Form" and "Industry 4.0 Conceptual Awareness Scale" were used to collect the data.

Sociodemographic Data Form

The form was developed in line with the literature to determine the socio-demographic characteristics of the students 18, 19.

Industry 4.0 Conceptual Awareness Scale

The Industry 4.0 Conceptual Awareness Scale is a 39-item, one-dimensional scale developed by Dogan and Baloglu (2020). The Cronbach's Alpha coefficient of the scale was found to be 0.96. Participants indicate their level of awareness for the scale on a 5-item Likert scale as "none=1, little=2, medium=3, very=4 and full=5". The lowest score is 39, and the highest score is 195. As the scores obtained from the scale increase, the awareness level of the participants increases 18. The Cronbach Alpha coefficient of the original scale was 0.96, and the Cronbach Alpha coefficient was 0.98 in this study.

Analysis of Data

The data obtained from the study were evaluated in SPSS (Statistical Package for Social Sciences) 22.0 package program. Descriptive analyses (number, percentage, mean, standard deviation, minimum, and maximum) were used in the evaluation of the data. In the study, $p<0.05$ was accepted as the significance limit. Parametric tests were used when the data conformed to the normal distribution, and nonparametric tests were used when the data did not conform. Descriptive statistical methods such as frequency, percentage, mean, and standard deviation were used to evaluate the study data.

Ethics Committee Approval

To conduct the research, the necessary permission was obtained from the Tokat Faculty of Health Sciences, and ethics committee approval (No. 158991, session no. 09, decision no. 44) was obtained from Tokat Gaziosmanpaşa University Social and Human Sciences Research Ethics Committee. Before the participants started to fill out the questionnaire form, an informed consent form section explaining the purpose of the research was added and asked for approval. In this way, informed consent was obtained from the individuals.

Results

The findings of the research, which aim to determine the industry 4.0 awareness of midwifery students, are given in this section. The average age of students participating in the study was 21.22±1.84 (min=18, max=29) years. 31.9% of the students were 2nd-year students in the Department of Midwifery. The mean grade point average of the students, according to the quadratic system, was 3.27±1.96 (min=1.50, max=3.40). 62.6% of the students graduated from Anatolian high school, and 66.5% are currently staying in a state dormitory. 52.9% of the students have their own computers, 100% use smartphones, and 60.7% use computers. Results showed that 92.6% of the students had access to the internet where they lived. The time students spent on the internet was 5.23±2.89 (min=1, max=24) hours. 72.4% of the students did not use wearable technology, and 43.2% used media sharing and instant messaging applications (Table 1).

The relationship between some characteristics of the students and the scores obtained from the scale was analyzed. This information is given in Table 2. There was no significant correlation between the students' grades, high school graduated from, owning a computer, using a computer, internet access at the place of residence, using wearable

technology, social media accounts used, grouped grade point averages, and the scores obtained from the scale (p> 0.05). When the relationship between the place where the students stayed and the scores obtained from the scale was examined, it was determined that there was a significant difference between the scores obtained from the scale by students staying in public dormitories and students staying in private dormitories (p< 0.05). When the source of the difference was examined through post-hoc analysis, it was determined that it was between students living in private dormitories and students living in public dormitories. Accordingly, it was determined that the scores obtained from the scale by students living in private dormitories were statistically higher (Table 2).

The average score of the students on the scale is 89.98 ± 30.5 (min=39, max=195). According to the score obtained from the scale, it was determined that the students' Industry 4.0 conceptual awareness was at a medium level.

Table 1. Descriptive statistics for some characteristics

Characteristics	Avg.±SS* (min-max)	
Age	21.22±1.84 (18-29)	
Time spent on the internet	5.23±2.89 (1-24)	
Average grade	3.27±1.96 (1.50-3.40)	
	n	**%**
Year		
1.year	52	20.2
2.year	82	31.9
3.year	65	25.3
4.year	58	22.6
Students' last high school graduated from		
Regular High School	26	10.1
Vocational and Technical Anatolian High Schools	35	13.6
Anatolian High School	161	62.6
Science High School	23	9
Other	12	4.7
Student's residence		
Public Dormitory	171	66.5
With Family	48	18.7
Student House	24	9.4
Private Dormitory	14	5.4
Owns a computer		
Yes	121	47.1
No	136	52.9
Uses a smartphone		
Yes	257	100
No	0	0
Uses a computer		
Yes	156	60.7
No	101	39.3
Internet access at the place of residence		
Yes	238	92.6
No	19	7.4
Uses wearable technology		
Yes	71	27.6
No	186	72.4
Social media accounts used		
Media sharing (tiktok, instagram, snapchat, youtube)	104	40.5
Instant messaging (whatsapp, telegram, signal)	5	1.9
Social media (twitter, facebook, linkedin)	6	2.3
Media sharing and social media	111	43.2
Media sharing and instant messaging	31	12.1
Total	257	100

Table 2. The relationship between some variables and the scores obtained from the scale

Characteristics	Total points	Test value
Year		
1.year	87.03±24.5	
2.year	87.24±30.7	F:0.825
3.year	92.29±29.0	p:0.481
4.year	93.91±36.1	
Students' last high school graduated from		
Regular High School	100.80±27.9	
Vocational and Technical Anatolian High Schools	90.91±31.7	F:1.650
Anatolian High School	87.36±32.2	p:0.162
Science High School	88.26±30.37	
Other	102.33±30.3	
Student's residence		
Public Dormitory	85.12±29.3[a]	**F:5.154**
With Family	96.50±31.7	**p:0.02**
Student House	100.54±25.8	
Private Dormitory	108.85±34.8[a]	
Owns a computer		
Yes	90.77±31.6	t:0.392
No	89.27±29.5	p:0.455
Uses a computer		
Yes	92.21±31.1	t:1.457
No	86.54±29.2	p:0.314
Internet access at the place of residence		
Yes	89.45±30.4	U:1993.5
No	96.63±31.1	p:0.391
Uses wearable technology		
Yes	94.70±30.4	F:0.15
No	88.18±30.4	p:0.902
Social media accounts used		
Media sharing (tiktok, instagram, snapchat, youtube)	91.25±28.6	
Instant messaging (whatsapp, telegram, signal)	87.00±33.2	KW:2.292
Social media (twitter, facebook, linkedin)	84.50±36.1	p:0.682
Media sharing and social media	87.88±32.4	
Media sharing and instant messaging	94.80±29.1	
Grouped grade point average		
2.50 and below	79.14±31.8	KW:0.459
Between 2.50 and 3.00	89.75±26.8	p:0.633
Between 3.00 and 4.00	90.37±31.1	

F:ONE WAY ANOVA, t:independent t test, KW: Kruskal Wallis, U: Mann-Whitney U
a: There is a significant difference between variables with the same letter within the group.

Table 3. Scale total mean score and Cronbach Alpha coefficient

Scale total mean score	Cronbach Alpha coefficient
89.98 ± 30.5(min=39,max=193)	0.98

Discussion

This study aimed to determine the level of Industry 4.0 conceptual awareness of midwifery students. According to the result obtained in the research, it was determined that the Industry 4.0 Conceptual Awareness level of 247 students in the sample group was at a medium level. When the literature was examined, no research was found to determine the Industry 4.0 conceptual awareness levels of students studying in Health Sciences. Dogan and Baloglu (2020) concluded that the Industry 4.0 conceptual awareness levels of Engineering and FEAS students were at a medium level [19]. However, the average score obtained from the scale was found to be higher than in this study. The reason for this is thought to be that students in these fields are intertwined with the concept of

Industry 4.0 within the scope of the courses they take. Kaygisiz and Sipahi (2019) conducted a study to examine the Relationship Between Individual Innovation and Industry 4.0 Knowledge Levels of Generation Y University Students; when we look at the sources where the students participating in the research obtained information about Industry 4.0, it was done through a course subject and websites [20]. Isa et al. (2021) concluded that students in Malaysia have low levels of perception and knowledge about Industry 4.0. However, it was observed that students were willing to improve their knowledge and skills related to Industry 4.0 [21]. Tinmaz and Hwa Lew (2019), in a study conducted with university students in South Korea, found that the participants were not very aware of Industry 4.0 [22]. According to the findings obtained from these studies, it is clear that changes are inevitable in higher education institutions in parallel with the development of Industry 4.0 technologies.

In the study, no significant relationship was found between the grade of the students and the scores obtained from the scale ($p > 0.05$). However, it was determined that the score obtained from the scale increased as the grade level increased. Dogan and Baloglu (2020) concluded that students' Industry 4.0 conceptual awareness levels did not change significantly according to class level [19]. Yelkikalkan et al. (2019) found that the perceived benefit levels and usage behaviors of the students regarding Industry 4.0 technologies showed a significant difference according to the classes they studied, while the perceived ease of use and intention to use did not show a significant difference according to the class they studied [3]. Motyl et al. (2017) conducted a two-semester survey on 463 students at the University of Brscia, the University of Udinese, and the University of Cassino in Italy to determine the skills and expertise required for young engineers to be ready for Industry 4.0 and found that 'as the students' grade increases, their conceptual awareness levels also increase' [23]. It is thought that the increase in their awareness of the concept of Industry 4.0 as the grade level increases creates awareness of this concept within the scope of the courses they take.

Moreover, no significant relationship was found in the study between the social media accounts used by the students and the scores obtained from the scale ($p > 0.05$). Yarim and Celik (2020), in the study titled The Necessity and Role of the Teacher from the Student's Perspective in the Age of Industry 4.0, when the findings related to the question "In which ways do you access the information you use in daily life?" are examined, it is seen that students mostly access the information they use in daily life from the internet (websites, blogs, search engines, educational sites, etc.) and virtual world (Twitter, Instagram, Facebook, etc.) [24]. According to the research findings, teachers and schools, which were the most important sources of obtaining information in the past, have lost their former importance in accessing information. Students can now easily access information whenever they want through the internet. However, it is seen that they need support on how to use this information. In this context, today's teachers have a role in helping students process and use information instead of delivering it.

Results showed that there was no significant relationship between the grouped grade point averages of the students and the scores obtained from the scale ($p > 0.05$). However, it was found that the score obtained from the scale increased as the grade point average increased, and the highest score from the scale was obtained by students with a GPA between 3-4. According to the results of Dogan and Baloglu's (2020) study, it was determined that the Industry 4.0 conceptual awareness levels of university students with a GPA between 3-4 were at a higher level compared to students in other grade ranges [19].

When the relationship between the place where the students stayed and the scores obtained from the scale was examined, it was determined that there was a significant difference between the scores obtained from the scale by the students staying in public dormitories and the students staying in private dormitories ($p < 0.05$). In the post hoc analysis, it was seen that the difference was in favor of the students staying in private dormitories. In the study conducted by Isik (2022) on the Determination of Awareness of Industry 4.0 Approach from the Perspective of University Students, when the results of the Tukey Test were analyzed according to the "Industry 4. 0 knowledge" factor, there is a significant difference between staying in dormitories and staying in hostels and staying with relatives; between staying in hostels and staying in dormitories, houses and staying in their own homes; between staying at home and staying in hostels, staying with relatives and staying in their own homes; between staying with relatives and staying in hostels, houses and staying in their own homes; between staying in their own homes and staying in hostels and staying in their own homes. Accordingly, it was determined that university students' knowledge about technological tools and Industry 4.0 differed significantly according to the place of residence

variable [25]. Similar findings were found with this study.

In the study, no significant correlation was found between the scores obtained from the scale and the students' status of having a computer of their own, using a computer, having internet access at the place of residence, and using wearable technology ($p > 0.05$). Yıldız and Fırat (2020) conducted a study to determine the Industry 4.0 knowledge level of university students in Turkey and found that students' perceptions and attitudes towards technology were insufficient to affect their Industry 4.0 knowledge level. In addition, university students' awareness and knowledge levels about Industry 4.0 technology and its components are insufficient to catch up with the speed and technologies of the revolution we are experiencing. Moreover, university students adopt and use products and conveniences reflected in daily life but are far from the concepts and technologies that form the infrastructure [26]. In this context, it can be said that although students have used Industry 4.0 technologies and components in their lives, this does not affect their Industry 4.0 awareness.

CONCLUSIONS

The conclusion shows that the level of Industry 4.0 Conceptual Awareness of midwifery students was at a moderate level, and the place of residence of the student positively affected the level of awareness of this concept. Based on the results obtained in the study, it is recommended to study the level of Industry 4.0 conceptual awareness in different sample groups. In addition, determining the level of Industry 4.0 conceptual awareness of university lecturers and administrators should also be addressed. The course contents of higher education institutions should be revised following the developments in this field, and necessary measures should be taken to increase the awareness levels of students. To increase awareness of Industry 4.0, it can be suggested that courses on Industry 4.0 and the digital revolution should be offered, informative activities such as conferences, seminars, etc. should be increased, and professional organizations and chambers should serve in this regard with different activities.

Ethics Committee Approval: Ethics committee approval (No. 158991, session no. 09, decision no. 44) was obtained from Tokat Gaziosmanpaşa University Social and Human Sciences Research Ethics Committee.

Informed Consent: Before the participants started to fill out the questionnaire, their informed consent was obtained with an informed consent form explaining the purpose of the study.

Disclosures: This research was presented as an abstract at the 1st International 1st National Digital World & Digital Health & Digital Midwifery Congress held on October 19-21, 2022.

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Research Limitations: Since the Industry 4.0 Awareness Scale used in the research has not yet been used in other studies in the field of midwifery, this caused limitations in the writing of the discussion section. In addition, since Industry 4.0 is a current issue, the limited knowledge of individuals in the society on the subject and the low level of awareness on this subject is another limitation of the research. The findings obtained from this research only cover the midwifery students included in the research and cannot be generalized to all students.

References

1. Karadayi Usta S. Industry 4.0 researches conducted in Turkey. Journal of Turkish Operations Management. 2021;5(2):839-61.
2. Ozsoylu AF. Industry 4.0. Journal of Cukurova University Faculty of Economics and Administrative Sciences. 2017;21(1):41-64.
3. Yelkikalan N, Ozcan S, Temel K. Determination of the industrial awareness: The case of Çanakkale Onsekiz Mart University. Journal of Entrepreneurship and Development. 2019;14(1):31-44.
4. Akgul H, Ayer Z. Change and transformation in occupations in Industry 4.0 process. Journal of History School (JOHS). 2020;45:1326-44.
5. Akalin B, Veranyurt U. Health 4.0 and artificial intelligence. Journal of Health Professionals Research. 2022;4(1):57-64.

6. Aslan S, Güzel S. Industry 4.0 development process and digital transformation in health. IBAD Journal of Social Sciences. 2019:650-9.
7. Sood SK, Rawat KS, Kumar D. A Visual review of artificial intelligence and industry 4.0 in healthcare. Computers and Electrical Engineering. 2022;101:107948.
8. Ahmad M, Sadiq S, Alluhaidan AS, Umer M, Ullah S, Nappi M. Industry 4.0 technologies and their applications in fighting covıd-19 pandemic using deep learning techniques. Computers in Biology and Medicine. 2022;145:105418.
9. Nollo G, Pilati F, Tronconi R, Rigoni M. Industry 4.0 at the service of public health against the covid-19 pandemic. Disaster Medicine and Public Health Preparedness. 2022;16(5):1735-6.
10. Roy S, Meena T, Lim S-J. Demystifying supervised learning in healthcare 4.0: A new reality of transforming diagnostic medicine. Diagnostics. 2022;12(10):2549.
11. Koşti G, Burmaoglu S, Kidak LB. Health 4.0: Projections of forecasted development in the industry on the health sector. Hacettepe Journal of Health Administration . 2021;24(3):483-506.
12. Sezer K, Gedik O. Moderating role of demographic properties on industry 4.0's effect on healthcare sector: An application using the technology acceptance model. Hacettepe University Journal of Economics and Administrative Sciences. 2020;38(4):743-76.
13. Alam SS, Masukujjaman M, Ahmad M, Jaffor R. Acceptance of online distance learning (ODL) among students: Mediating role of utilitarian and hedonic value. Education and Information Technologies. 2022:1-34.
14. Torun NK, Cengiz E. The perspective of university students' through the technology acceptance model (TAM) to industry 4.0. International Journal of Economic and Administrative Studies. 2019;(22):235-50.
15. Öner S. The development and evaluation of a virtual reality simulation to teach the first care of a newborn doctoral thesis. Izmir: Ege University; 2020.
16. Ozkoçak Tuna F, Divlek N, Karahan N, Kiziltepe K, Engin Üstün Y. Evaluation of the virtual field experience training program accompanied with simulation for students who cannot complete clinical practice training during the pandemic process: A retrospective review (Etlik Zübeyde Hanım Gynecology Training and Research Hospital Online Education Model Example). Turkish Journal of Women's Health and Neonatology. 2023;5(1):6-13.
17. Maylawati DSa, Ramdhani MA, Zulfikar WB, Taufik I, Darmalaksana W, editors. Expert system for predicting the early pregnancy with disorders using artificial neural network. 2017 5th International Conference on Cyber and IT Service Management (CITSM); 2017: IEEE.
18. Dogan O, Baloglu N. Industrial 4.0 Conceptual Awareness Scale. Karamanoglu Mehmetbey University Journal of Social and Economic Research. 2020;22(38):58-81.
19. Doğan O, Baloglu N. Industrıal 4.0 conceptual awareness levels of university students. TUBAV Journal of Science. 2020;13(1):126-42.
20. Kaygisiz EG, Sipahi H. The investigation of the relationship between individual innovation and industry 4.0 knowledge levels of Y generation university students. Gaziantep University Journal of Social Sciences. 2019;18(2):922-36.
21. Isa K, Rosni N, Palpanadan ST. Malaysian University students'perceptions and knowledge level of industrial revolution 4.0. Academy of Education Journal. 2021;12(2):169-78.
22. Tinmaz H, Hwa Lee J. A Preliminary Analysis on Korean University students' readiness level for Industry 4.0 revolution. Participatory Educational Research. 2019;6(1):70-83.
23. Motyl B, Baronio G, Uberti S, Speranza D, Filippi S. How will change the future engineers' skills in the Industry 4.0 framework? A questionnaire survey. Procedia manufacturing. 2017;11:1501-9.
24. Yarim MA, Celik S. Teacher's role and the necessity from the perspectives of the students in Industrial 4.0 age. Mehmet Akif Ersoy University Journal of Social Sciences Institute. 2020;(31):76-92.
25. Isik I. Determining the awareness of university students for the industrial 4.0 approach: Example of Aydin master's thesis. Aydin: Aydin Adnan Menderes University; 2022.
26. Yildiz SC, Firat SU. Investıgatıon of Industry 4.0 knowledge level of university students in Turkey. Journal of Industrial Engineering. 2020;31:1-16.

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Broccoli (Brassica oleracea var. italica) extract's potential therapeutic targets on human breast cancer (MDA-MB-231) using the AgNOR detection method

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Research Article

History

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ABSTRACT

Background: In this study, the in vitro effect of the extract obtained from mature broccoli on the breast cancer cell line was aimed to be determined.MDA-MB-231 cells were exposed to broccoli extract at 37°C and 5% CO2 for different durations (24 and 48 hours) and doses (125 and 250 µl/ml). At the end of the incubation period, the viability, apoptosis, cell cycle, and AgNOR protein status of MDA-MB-231 cells were examined using the Muse Cell Analyzer.In the groups treated with broccoli extract, a decrease in the percentage of viable cells and a significant increase in the percentage of early and total apoptosis were observed for both doses compared to the control group. In the cell cycle analysis, there was an increase in the number of cells in the S phase in all the groups. It was observed that the groups treated with broccoli extract caused a delay in the cell cycle progression at the transition to the S checkpoint. AgNOR staining results further supported the cell cycle and apoptosis findings. The AgNOR number and TAA/NA ratio decreased in the 125 µl/ml broccoli extract group after 24-48 hours and were found to be statistically significant compared to the control group. It was determined that broccoli extract induced apoptosis in breast cancer cells through various mechanisms and inhibited cell viability and growth. These results were consistent with the findings related to AgNOR protein synthesis.
The study demonstrated that the consistent and proper consumption of broccoli may be effective in preventing cancer formation and slowing its progression.

Keywords: Diabetic nephropathy, microalbuminuria, serum uric acid/creatine ratio

Brokoli (Brassica oleracea var. italica) Ekstraktının İnsan Meme Kanseri Hücrelerine (MDA-MB-231) Etkisi ve AgNOR Tespit Yöntemi ile Analizi

Süreç

Geliş: 07/01/2023
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ÖZ

Arka Plan: Bu çalışmada, olgun brokolinin ekstraktının meme kanseri hücre hattı üzerindeki in vitro etkisinin belirlenmesi amaçlanmıştır.MDA-MB-231 hücreleri, 37°C ve %5 CO2'de farklı süreler (24 ve 48 saat) ve dozlar (125 ve 250 µl/ml) için brokoli ekstraktına maruz bırakıldı. İnkübasyon süresinin sonunda, MDA-MB-231 hücrelerinin canlılık, apoptozis, hücre döngüsü ve AgNOR protein durumu Muse Hücre Analizörü kullanılarak incelendi.
Brokoli ekstraktı ile tedavi edilen gruplarda, canlı hücre yüzdesinde bir azalma ve erken ve toplam apoptozis yüzdesinde kontrol grubuna göre anlamlı bir artış gözlendi. Hücre döngüsü analizinde, tüm gruplarda S fazındaki hücre sayısında bir artış gözlendi. Brokoli ekstraktı ile tedavi edilen grupların, S kontrol noktasına geçişte hücre döngüsü ilerlemesinde bir gecikmeye neden olduğu gözlendi. AgNOR boyama sonuçları, hücre döngüsü ve apoptozis bulgularını daha da destekledi. 24-48 saat sonra 125 µl/ml brokoli ekstraktı grubunda AgNOR sayısı ve TAA/NA oranında azalma gözlendi ve kontrol grubuna göre istatistiksel olarak anlamlı bulundu. Brokoli ekstraktının, meme kanseri hücrelerinde çeşitli mekanizmalar aracılığıyla apoptoza neden olduğu ve hücre canlılığını ve büyümesini inhibe ettiği belirlendi. Bu sonuçlar, AgNOR protein sentezi ile ilgili bulgularla tutarlıydı. Çalışma, brokolinin tutarlı ve uygun tüketiminin, kanser oluşumunu önlemede ve ilerlemesini yavaşlatmada etkili olabileceğini göstermiştir.

Anahtar sözcükler: Diyabetik nefropati, mikroalbünüri, serum ürik asit /creatin oranı

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Introduction

Cancer is a highly lethal disease characterized by uncontrolled cell proliferation and invasive metastasis. It stands out as a leading cause of death and a significant public health issue in many countries, driven by rapid population growth and an aging population worldwide. Breast cancer is the most prevalent cancer type among women in Turkey and worldwide.1 Chemotherapy is a widely employed cancer treatment method, with most anticancer drugs used in chemotherapy exerting cytotoxic properties that inhibit cancer cell growth and proliferation. However, these drugs also harm healthy cells and tissues due to their harmful properties. To mitigate drug side effects and enhance their effectiveness, research is being conducted to develop more specific inhibitory compounds. Epidemiological and pathological studies suggest that cancers can be prevented or their progression halted.2 Dietary fruits and vegetables, in particular, have garnered significant attention due to their low toxicity and have been recognized as rich sources of chemopreventive compounds. Diets rich in fruits and vegetables have been shown to significantly reduce the risk of developing breast cancer, as well as lung, esophagus, larynx, pancreatic, colorectal, stomach, and prostate cancers.3 Broccoli (Brassica oleracea L. var. italica, Brassicacae) is an excellent source of isothiocyanates and is also abundant in vitamins (β-carotene, K, C), polyphenols, fatty acids, and dietary fiber. Various forms of broccoli, such as sprouts, powder, flour, fiber, florets, flakes, chips, etc., are gaining considerable attention today due to their preventive roles in non-communicable diseases like atherosclerosis, cancer (breast, prostate, lung, pancreas), and hypertension.4-7 In recent times, cell culture studies have become increasingly important, particularly in expediting cancer research, developing anticancer drugs, and assessing their effects. Nucleolar organizing regions (NORs) are loops of DNA containing ribosomal gene domains. As protein synthesis takes place in ribosomes within cells, ribosomes and the ribosomal RNA (rRNA) component are essential. The nucleolus houses extensive DNA loops, known as NORs, which transcribe RNA genes via RNA polymerase I. These loops of DNA are referred to as NORs. In normal cells, only a portion of rDNA is present in their nucleoli, but during rapid cell proliferation, there is an increased amount of rDNA within the nucleoli.8 Genetically active NORs can be stained using silver staining. NOR staining, also known as "silver staining," is a technique used to visualize and differentiate regions forming nucleoli at various stages of interphase or the cell cycle in various plant and animal tissues. When proteins within NORs are stained using the silver staining technique, they appear as dark brown-black spots within the cell nucleus.9,10 Previous studies have yielded positive results indicating that broccoli inhibits cancer progression by inducing apoptosis in cancer cells or arresting the cell cycle. Furthermore, there is currently no study in the literature investigating the antitumoral effects of broccoli on human breast cancer (MDA-MB-231) using AgNOR staining methods. In this study, we aimed to demonstrate the apoptotic effect of broccoli on MDA-MB-231 breast cancer cell lines and its potential impact on AgNOR protein synthesis. Additionally, we sought to determine the most appropriate dosage for cancer treatment.

Material Method

Preparation of Broccoli Extract: Three mature broccoli plants were procured from a local market in Kayseri for use in the study. On the day of acquisition, the broccoli was thoroughly washed and cut into pieces. Broccoli juice was then obtained by juicing the pieces using a juicer (Arçelik, K-1579, China). The resulting juice was collected in a glass jar and transported to the Erciyes University Anatomy Department Laboratory, where it was stored at a constant temperature of +4 ºC.

The samples were subsequently transferred to 50 ml centrifuge tubes. To remove the pulp, the samples were centrifuged four times for 15 minutes each at 5000 rpm using a centrifuge device (Selecta, Spain).

In order to eliminate macromolecules from the broccoli juice, it was first passed through a filter with a pore diameter of 0.45 µm and then through a filter with a pore diameter of 0.22 µm. Following this process, 28 ml of broccoli extract was obtained, which was then divided into four 7 ml beakers. The tops of the beakers were sealed with parafilm, and the extracts were stored in the dark at –20°C. After pretreatment, the frozen samples were placed in a lyophilizer (CHRIST) for drying. Lyophilization was conducted at -50 ºC under conditions of >0.065 mbar, lasting for 24 hours. The powdered broccoli was removed from the beaker and weighed on a precision balance (RADWAG) on aluminum foil. A total of 1.16 g of powdered broccoli was obtained from the broccoli juice. The resulting extract was stored at -20 ºC until further analysis.

Cell Culture: The MDA-MB-231 cell line was obtained from the American Type Culture Collection (Manassas, VA, USA). MDA-MB-231 cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) (Capricorn Scientific, CP21-4310) supplemented with streptomycin/penicillin (100 U/ml; Sigma Life Science, 046M4846V) and 15% fetal calf serum (FCS) (Biowest, S181G-500) in a humidified incubator (Sanyo, MCO-19 A/C(UV)) with an atmosphere of 5% CO2 at 37°C. Sterile conditions were strictly maintained to prevent the risk of contamination.

Healthy MDA-MB-231 cells were then divided into groups for broccoli treatment. Tissue culture plates with 24 wells, each containing 1000 µL of medium with 1×105 MDA-MB-231 cells, were used to determine the optimal broccoli dosage. These MDA-MB-231 cells were cultured in a humidified atmosphere containing 95% air and 5% CO2 overnight to allow attachment to the plates. After removing the medium, the MDA-MB-231 cells were washed three times with 500 µL of phosphate-buffered saline (PBS). Subsequently, the MDA-MB-231 cells were identified, and experimental groups were established using logarithmic concentrations of broccoli (125 and 250 µL/ml) applied to breast cancer cells after varying culture periods.

Cell Viability Assay and Proliferation: The cell suspension's concentration, expressed as cells per ml, was determined using the Trypan Blue cell counting method. To perform cell counting, a volume of the cell suspension was pipetted into an Eppendorf tube, and an equal volume of Trypan Blue solution was added. After 5 minutes of incubation, the mixture was placed between both sides of a closed Thoma slide (Marienfeld-Superior). Stained and unstained cells were counted using a microscope (Nikon Eclipse TS100). The average number of cells within the counting area was calculated, and the number of viable cells (cells/ml) was determined using the formula: Number of viable cells (cells/ml) = Average number of cells x 2x104.

Experimental Design: Experimental groups were established for Annexin V assays with 24-hour and 48-hour incubation periods, including a control group, as well as for cell cycle testing, which included the 125 µL/ml and 250 µL/ml broccoli treatment groups.

Annexin V Assay: Apoptosis analysis was conducted using the Muse Cell Analyzer device along with the compatible Muse Annexin V kit and dead cell assay reagent (Millipore; MCH100115).

MDA-MB-231 cells were seeded in 24-well plates at a density of 1x105 cells per well and allowed to incubate for 24 and 48 hours. Subsequently, the cells were treated with trypsin and stained with Annexin V and the dead cell reagent following the manufacturer's protocols (Millipore Corporation). The stained cells were then analyzed using the Muse Cell Analyzer (Millipore Corporation)

Cell Cycle Assay: The MuseR Cell Cycle Kit (Millipore; MCH100106) was employed to determine the cell cycle stage of the cells.

MDA-MB-231 cells were seeded in 24-well plates at a density of 1x106 cells per well and allowed to

incubate for 24 and 48 hours. Subsequently, the cells were treated with trypsin to detach them. Following detachment, the cells were stained with the MuseR Cell Cycle Kit, following the manufacturer's protocols (Millipore Corporation). The stained cells were then analyzed using the Muse Cell Analyzer (Millipore Corporation)

AgNOR Staining: MDA-MB-231 cells cultured in the presence of 125 µg/ml and 250 µg/ml broccoli, as well as control and treated groups, were spread onto clean slides and allowed to air dry at room temperature. After air drying, the slides were fixed in a fixative solution (3 volumes methyl alcohol:1 volume acetic acid), and the AgNOR staining method was conducted following a slightly modified version of the protocol as outlined by Lindler.11 The AgNOR-stained slides were examined using a light microscope (Leica DM 3000) and photographed with a digital camera (Imaging Color 12 BIT, Made in Canada).

The captured images of MDA-MB-231 cells were transferred to image processing software (ImageJ version 1.47t, National Institutes of Health, Bethesda, Maryland, USA), and both the total AgNOR area per nuclear area (TAA/NA) and mean AgNOR number were calculated using the 'freehand selection' tool for each nucleus. Fifty nuclei were assessed for each slide. An illustrative example of AgNOR staining of MDA-MB-231 cells is presented in Figure 1.

Statistical Analysis: The data's adherence to a normal distribution was assessed using the Shapiro-Wilk test, histograms, and q-q plots. One-way analysis of variance (ANOVA) was employed to statistically compare parameters across groups. The homogeneity of variances in the data was assessed using the Levene test. Multiple comparisons were performed using the Tukey test. Within each group, differences between the 24-hour and 48-hour measurements were assessed using the paired t-test. Data analysis was conducted using the Turcosa statistical software (Turcosa Analytics Ltd Co, Turkey, www.turcosa.com.tr). A p-value of <0.05 was considered statistically significant..

Results

Results

Annexin V and Dead Cell Test Results: In the graphs generated by the Muse device, four quadrants were formed by the intersection of the horizontal and vertical axes. Cell populations corresponding to different markers were observed in these quadrants. Dead cells were identified in the upper left quadrant, living cells in the lower left quadrant, late apoptotic cells in the upper right quadrant, and early apoptotic cells in the lower right quadrant. The data graphs obtained from the Muse Cell Analyzer device at the end of the 24 and 48-hour incubation periods are presented in Figure 2 and Figure 3.

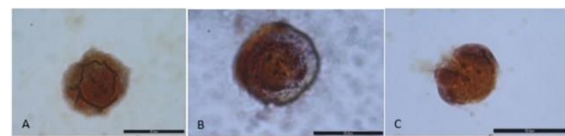

Figure 1. Demonstrative example of AgNOR staining of MDA-MB-231 cells. A: Control, B: 125 µl/ml broccoli, C: 250 µl/ml broccoli.

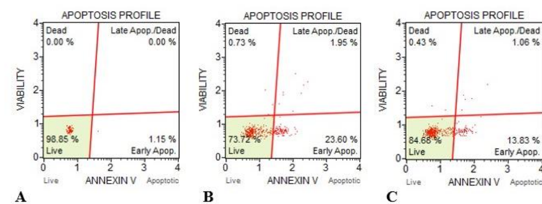

Figure 2. Data plots of 24-hour apoptosis rates by group on the Muse Cell Analyzer. A. Control group B. 125 µL broccoli extract, C. 250 µL broccoli extract.

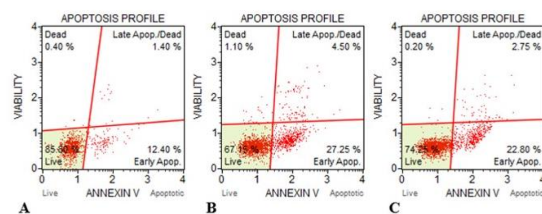

Figure 3. Data graphs of 48-hour apoptosis rates by groups on the Muse Cell Analyzer device. A. Control

group, B. 125 µl broccoli extract, C. 250 µl broccoli extract.

When the results related to viable cells were evaluated within the groups depending on the incubation period, a statistically significant difference was observed in the control group and the 250 µL/ml broccoli group ($p<0.05$), while no significant difference was found in the 125 µL/ml broccoli group. When the groups were evaluated based on the dose at 24 and 48 hours, a significant difference was found in all groups ($p<0.05$). Significant differences were also observed in the pairwise comparisons between the control group, 125 µL/ml, and 250 µL/ml groups in terms of viable cell counts at 24 and 48 hours ($p<0.001$). The most significant decrease in viable cell count was observed in the 125 µL/ml broccoli group.

There was no statistically significant difference in the number of early apoptotic cells when the results regarding early apoptotic cells were evaluated depending on the incubation period within the groups. However, a statistically significant difference was found in the number of early apoptotic cells when evaluated based on the dose at 24 and 48 hours ($p<0.05$). It was observed that the percentage of early apoptotic cells increased in the 125 and 250 µL/ml groups compared to the control group. According to multiple comparison tests, significant differences were found in the number of apoptotic cells at 24 hours between the control, 125 µL/ml, and 250 µL/ml groups ($p<0.001$). Based on these results, the 24-hour 125 µL/ml broccoli group exhibited the most significant increase in early apoptosis.

When the results regarding the percentage of late apoptotic cells were evaluated within the groups depending on the incubation period, a statistically significant difference was observed in the control and 125 µL/ml groups ($p<0.05$), while no significant difference was found in the 250 µL/ml group. When the groups were evaluated for the number of late apoptotic cells based on the dose, a significant difference was found at the 24-hour time point ($p<0.05$), but no significant difference was observed at the 48-hour time point. According to the multiple comparison test, the number of late apoptotic cells at 24 hours was significantly lower in the control group compared to the 250 µL/ml group ($p<0.05$).

When the total number of apoptotic cells was evaluated within the groups based on the dose, a significant difference was found at both the 24-hour and 48-hour time points ($p<0.05$). However, when the groups were evaluated depending on the incubation period, a significant difference was observed in the total number of apoptotic cells only in the control group ($p<0.05$), while no significant difference was found in the other groups ($p>0.05$). Multiple comparison tests revealed significant differences in the total number of apoptotic cells between all groups at 24 and 48 hours ($p<0.05$). The 125 µL/ml broccoli group exhibited the most significant increase in total apoptotic cells.

Cell Cycle Test Results: The data graphs obtained from the Muse Cell Analyzer device at the end of the 24 and 48-hour incubation periods are presented in Figure 4 and Figure 5.

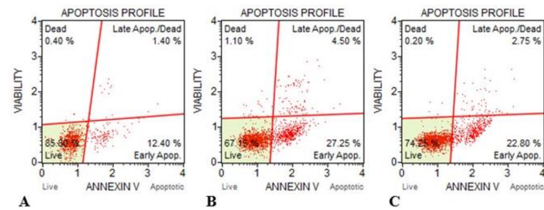

Figure 4. Data graphs of the percentage distribution ratios of the 24-hour cell cycle phases by groups, as read in the Muse Cell Analyzer device. A. Control group B. 125 µL broccoli extract C. 250 µL broccoli extract.

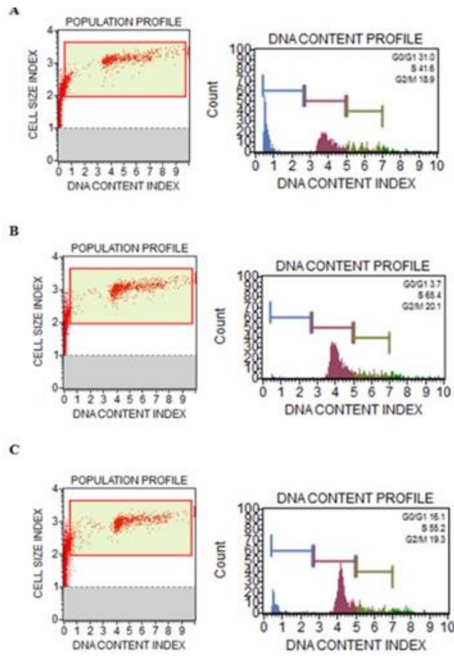

Figure 5. Data graphs of the percent distribution rates of 48-hour cell cycle phases by groups, as read in the Muse Cell Analyzer device. A. Control group B. 125 µL broccoli extract C. 250 µL broccoli extract.

When the results at 24 hours were evaluated, it was observed that the proportions of cells in the G0/G1 stage were lower in the 125 and 250 µL/ml groups compared to the control group ($p<0.05$), but there was no significant difference at 48 hours. When the groups were evaluated based on the dose, a significant difference was found in all groups at the G0/G1 stage ($p<0.05$) at both time points. Multiple comparison tests indicated significant differences in cell count measurements at 24 hours between all groups ($p<0.05$).

A significant dose-related difference was observed between the groups in the evaluation of cell cycles in the S stage at both the 24-hour and 48-hour time points ($p<0.05$). When the groups were evaluated based on the incubation period, a significant difference was found in all groups in the S phase at both time points ($p<0.05$). Multiple comparison tests revealed significant differences in S stage cell measurements at 24 and 48 hours between all groups ($p<0.05$).

In the evaluation of cell cycles at 24 and 48 hours, there was no significant dose-related difference between the groups. However, when the groups were evaluated based on the incubation period, a significant difference was observed in all groups in the G2/M stage ($p<0.05$).

AgNOR Results: The Total AgNOR Area/Nuclear Area (TAA/NA) ratio and mean AgNOR number were determined in the broccoli (125 and 250 µg/ml) groups and the control group.

As a result of the analysis, it was found that the AgNOR number (Table 1) and TAA/NA ratio (Table 2) significantly decreased at a dose of 125 µg/ml after 24 hours compared to the control group, and this difference was statistically significant ($p<0.05$) (Figure 6).

After 48 hours, the AgNOR number (Table 1) and TAA/NA ratio (Table 2) at a dose of 125 µg/ml also decreased compared to the control group and were found to be statistically significant ($p<0.05$) (Figure 7).

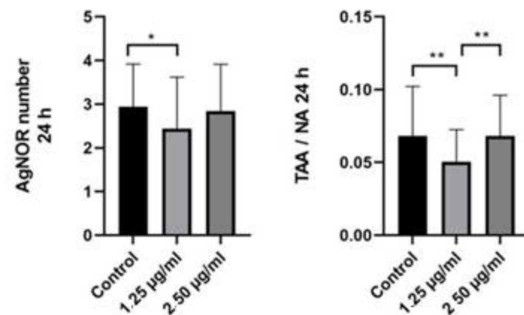

Figure 6. Comparison of AgNOR number and TAA/NA ratio between groups after 24 hours of incubation.

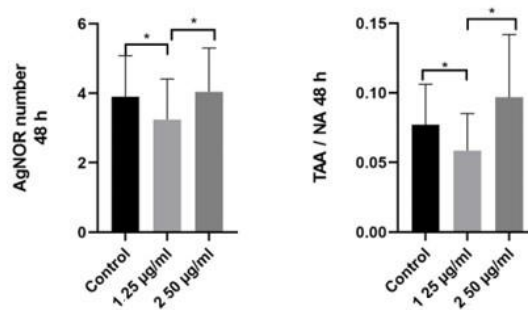

Figure 7. Comparison of AgNOR number and TAA/NA ratio between groups after 48 hours of incubation.

Table 1

Mean AgNOR number after 24 and 48 hours of incubation.

Hours/Groups	Control	125 µg/ml	250 µg/ml	*p*
24 hours	2,94±0,97[a]	2,44±1,18[b]	2,84±1,07[ab]	<0.001
48 hours	3,90±1,18[a]	3,24±1,17[b]	4,04±1,26[ab]	<0.001

AgNOR: Argyrophilic nucleolar organizer region

p<0.05 was considered statistically significant. Data are expressed as mean ± SD (Standard Deviation). Values with different letters (a and b) (p<0.05) in the same row at in-group measurement times were considered significantly different.

Table 2

TAA/NA value at the end of 24 and 48 hours of incubation.

Hours/Groups	Control	125 µg/ml	250 µg/ml	*p*
24 hours	**0,07±0,03[a]**	**0,05±0,02[b]**	**0,07±0,03[a]**	**<0.001**
48 hours	**0,08±0,03[a]**	**0,06±0,03[b]**	**0,09±0,04[a]**	**<0.001**

TAA/NA:Total AgNOR area/Nuclear area

p<0.05 was considered statistically significant. Data are expressed as mean ± SD (Standard deviation). Values having different letters (a and b) (p<0.05) on the same row at in-group measurement times were considered to be significantly different.

Discussion

Cancer treatment methods, including surgery, radiotherapy, hormone therapy, chemotherapy, and immunotherapy, often come with significant side effects. Therefore, there is a growing need to identify safe and potent anti-cancer compounds from natural sources.[12]

Epidemiological studies have consistently shown that a diet rich in fruits and vegetables can significantly reduce the risk of various types of cancer, including breast cancer.[13,14] Vegetables from the Brassicaceae family, such as broccoli, are particularly rich in chemopreventive compounds. Phytochemicals and their precursors found in these vegetables have demonstrated the ability to reduce the risk of cancer development.[15]

One such compound found in broccoli is sulforaphane (SFN), which has been extensively studied for its anti-cancer properties. SFN can inhibit phase I enzymes responsible for converting procarcinogens into carcinogens, and it can stimulate phase II enzymes, aiding in the detoxification and removal of carcinogens from the body. SFN has shown promise in preventing cancer initiation and progression by blocking the cell cycle or inducing apoptosis.[16]

Numerous studies have investigated the anti-cancer effects of SFN, often isolated from broccoli and other cruciferous vegetables, in various cancer types, including melanoma, prostate cancer, and pancreatic cancer. SFN has been shown to inhibit cell viability, induce apoptosis through the activation of genes like caspase 3 and 9, and interfere with signaling pathways such as NF-κB. It has also demonstrated the ability to overcome resistance to chemotherapy drugs like doxorubicin.[18,19] Oral or intraperitoneal administration of SFN inhibited tumor growth in prostate PC-3 and pancreatic Panc-1 xenografts.[20] It has been shown that the risk of premenopausal breast cancer is

inversely proportional to broccoli consumption.[15] Oral SFN reached the mammary gland and increased the detoxification enzyme activity.[21] By interfering with NF-κB-induced anti-apoptotic signaling, SFN has demonstrated the efficacy of abolishing pancreatic tumor resistance to TNF-related apoptosis-inducing ligand (TRAIL).[22,23] Another study showed that SFN can overcome doxorubicin resistance and restore apoptosis induction in cells.[24,25] These findings provide a strong rationale for investigating the chemopreventive property of SFN, broccoli, and broccoli sprouts in clinical trials.

Licznerska et al.[24] showed that MDA-MB-231 and MCF-7 breast cancer cell lines induced apoptosis after 72 hours of treatment at 5 and 20 µM SFN concentrations.

Lewinska et al.[25] stimulation of breast cancer cells (MDA-MB-231, SK-BR-3 and MCF-7) with low doses of SFN (5-10 µM) inhibits cell cycle, increases p21 and p27 levels and promotes cellular senescence, 20 µM It has shown that apoptosis is induced at this concentration.

Licznerska et al.[26] evaluated the effect of R-SFN on phase II enzyme induction and expression of AhR, Nrf2 and Erα, NQ01 in breast cell lines. Induction of NQO1 by R-SFN has been found to support treatment with certain chemotherapeutics in MDA-MB-231, while in non-tumorigenic cells representing the early stage of breast carcinogenesis and partially MCF7 cells, R-SFN protects against cancer initiation and progression.

The present study evaluated the effects of SFN and broccoli extracts on breast cancer cells, specifically MDA-MB-231 cells. Previous research has indicated that low doses of SFN can induce apoptosis, inhibit the cell cycle, increase levels of proteins like p21 and p27, and promote cellular senescence in breast cancer cells. SFN has also been explored as a potential histone deacetylase (HDAC) inhibitor in breast cancer, showing inhibitory effects on cell growth and proliferation. It reduced the expression of key proteins involved in breast cancer proliferation. These results support in vivo testing of SFN and warrant future studies examining the clinical potential of SFN in human breast. One of the recent studies has shown that 5, 25 and 100 µm ITC cause cytotoxic effects (reduction in viable cell count) in MCF-7 cells in vitro by altering DNA damage and repair-associated proteins.[27]

Pasko et al.[28] in a study comparing the apoptotic effect of broccoli sprouts and flowers, obtained broccoli (5 g) extracts by freeze-drying and dissolved the powdered broccoli in DMSO. In BJ, SW480, HepG2 cells 0.25, 1 and 2.5 mg/ml broccoli were incubated for 24 hours and Annexin V test was performed. It was found that the sprouts were more effective than the flowers and the 2.5 mg/ml broccoli dose had a significant effect on apoptosis on colorectal cancer cells. The doses of broccoli powder extracts whose apoptotic effects against MDA-MB-231 cell will be examined. The study was determined according to the pilot study conducted with reference to the study. When the literature was evaluated, SFN, which is the active ingredient of broccoli in cell culture

studies, was determined using high performance liquid chromatography (HPLC). However, SFN could not be determined in this study due to lack of equipment. Broccoli extracts were dried and powdered and dissolved in the medium and given to the cells. For this reason, it is thought that the result obtained is due to the bioactive components in broccoli, especially SFN. Since pure SFN cannot be used in basic nutrition, it is thought that this effect should be achieved by naturally fortifying cruciferous vegetables.

The effects of many herbal extracts on cancer cell lines are being investigated. In such studies, it has been shown that the percentage of total apoptotic cells increases as a result of Annexin V analysis[29,30] In this study, MDA-MB-231 cells were cultured for 24 and 48 hours at 37^0C and 5% CO_2, and the parameters obtained using Annexin V and cell cycle test were evaluated to determine the percentage of apoptosis. After 24 and 48 hours, it was found that the percentage of apoptosis on MDA-MB-231 cells increased and there was a significant decrease in the percentage of viable cells ($p<0.05$).

A significant increase was observed in the % total apoptosis rate in the MDA-MB-231 cell line cultured with broccoli compared to the control group. However, the increase was not significant over time. The percentages of early apoptosis rate were significantly increased in all groups compared to the control group. However, no statistically significant results were found depending on time. Late apoptotic responses were lowest in the 24-hour control group ($p<0.05$).

Stopping phases in the cell cycle can inhibit the proliferation of cancerous cells. This was realized by some phytochemical products and significant results were found.[31]

In an other study that investigated the effects of SFN on BALB/c mouse kidney cancer cells in vivo and in vitro, 15 µM SFN inhibited the cell cycle in the early phase of G2M (prophase/prometaphase) in 24 hours in the cell cycle test.[31]

Cheng et al.[32] were determined that in vitro study in which ZR-75-1 cells were treated with different concentrations of SFN (0, 6.25, 12.5, and 25 µM) for 24-72 hours, SFN after 24 hours, It has been shown to cause an increase in the G1 phase cell population, resulting in a delay in the G1/S phase checkpoint of ZR-75-1 cells. This result showed that SFN increased cell populations in the G1/S phase while simultaneously decreasing the S phase population.

Rutz J. et al.[33] in his study, it was observed that 5 µM SFN exposure increased the number of cells in the S phase of the cell cycle in Caki-1 and A498 cells and decreased the number of cells in the G0/G1 phase. When Caki1 cells were treated with 20 µM SFN, it was observed that the number of cells increased in both S and G2/M stages.

Experiments on osteosarcoma cells showed that SFN was effective in the G2/M phase at concentrations of ≤10 µM, while it was effective in the S phase at concentrations of >10 µM.[34]

Previous studies have shown that SFN can induce cancer cell apoptosis and cell cycle arrest.[31-35] In the current study, the 24th and 48th hour results showed a statistically

significant increase in cell count in the S phase of the broccoli extract ($p<0.05$). The most significant increase was seen in the number of cells in the S phase. This suggested that broccoli extract could effectively stop cancer cells in S phase. Rutz et al.[33] observed the effect of SFN on the cell cycle in ZR-75 human breast cancer cells and observed an increase in the number of cells in the S phase and G2M phase. The results of this study support the present study.

In the G0/G1 phase, there was a significant decrease in the groups containing broccoli extract compared to the control group ($p<0.05$). While the most significant decrease in the number of cells in the G0/G1 phase was observed in the group containing 125 µl/ml broccoli extract, the most significant increase in the number of cells in the S phase was observed in the 125 µl/ml broccoli extract groups. In the G0/G1 phase, the cells are stopped at the G1 to S checkpoint transition by suppressing the function of the complex formed by Cyclin E and Cyclin Dependent Kinase -2, which are the main cell cycle regulators, to promote cell transition from the G1 phase to the S checkpoint.[35] Based on this, it was thought that broccoli extracts slowed down the cell cycle at the G1 to S checkpoint transition in MDA-MB-231 cells. A significant difference was found in the 125 µg/ml broccoli extract group after 24 and 48 hours of incubation in AgNOR staining ($p<0.05$).

During the interphase, NORs are associated with a great number of regulatory proteins and they have roles as functional subunits of the nucleolus. Alterations in AgNOR protein amounts also reflect the metabolic activities of the cells. We performed various numbers of studies on malign and benign lesions.[36,37] In these studies, we evaluated mean AgNOR number and TAA/NA ratio as a new approach that may contribute to routine cytopathology for determining the proliferation activity of cells in malignant and benign lesions. In the current study, we aimed to identify whether broccoli has an effect on cell proliferation and whether the detection of AgNOR protein amounts may be used to detect the therapeutic benefits of the drugs and new metabolites that have a potential to be used in cancer treatments. The current study showed that the expression capacity of rRNA gene, as detected via total TAA/NA and/or AgNOR number per total nuclear number, decreased 125 µg/ml broccoli extract group. It may be said that broccoli has an important role in prevention of tumor formation and triggers or supresses the synthesis of some other proteins that have important features and functions in signaling the transduction pathways and gene expression regulation in tumor cells.

The study involved assessing apoptosis and cell cycle progression in MDA-MB-231 cells cultured with broccoli extract. Results showed a significant increase in apoptosis and a decrease in viable cells, with early apoptosis being most prominent in the group treated with 125 µl/ml broccoli extract at 24 hours.

Cell cycle arrest is another mechanism by which anti-cancer compounds can inhibit the proliferation of cancer cells. The current study observed that broccoli extract effectively arrested MDA-MB-231 cells in the S phase of the cell cycle. This

suggests that broccoli extract may be effective at halting cancer cell progression.

In summary, this research contributes to the expanding body of evidence that highlights the potential anti-cancer properties of SFN and broccoli extracts. Although this study did not pinpoint the exact mechanism of action or identify the specific active ingredient responsible for these effects, the findings strongly indicate that including broccoli and its bioactive components in one's diet could offer protection against breast cancer. Further investigations, including clinical trials, are necessary to delve deeper into the chemopreventive qualities of broccoli and its extracts.

The most important limitation of the study is; the content analysis of broccoli cannot be performed and the effective dose of its active ingredient, SFN, cannot be shown. In addition, it is not known under what conditions the broccoli used was stored until it was obtained.

Conclusion

Numerous studies have provided compelling evidence supporting broccoli as a potential anticancer agent, demonstrating its ability to inhibit the proliferation of various cancer cell lines, including those associated with the liver, stomach, colon, bladder, kidney, breast, and prostate. This specific study focused on evaluating the effects of powdered broccoli extracts obtained from different concentrations of broccoli juice on MDA-MB-231 cells.

The results of the study revealed that the broccoli extract led to a decrease in the number of viable cells, a significant increase in both early and total apoptosis, and a deceleration of the cell cycle during the transition from the G1 to S checkpoint ($p<0.05$). These findings align with prior research on apoptosis, suggesting that broccoli induces apoptosis in cancer cells through a variety of mechanisms, with the most pronounced effect observed in the 125 µL/ml broccoli group. Furthermore, the study demonstrated a reduction in the synthesis capacity of AgNOR proteins in the 125 µL/ml broccoli group, implying that broccoli may contain essential molecules for cancer prevention. Additionally, the research proposed that assessing the TAA/NA ratio could serve as a biomarker to evaluate the efficacy of therapeutic approaches and determine the most suitable dosage for cancer treatment.

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References

1. Ozmen V, Boylu S, Ok E, et al. Factors affecting breast cancer treatment delay in Turkey: a study from Turkish Federation of Breast Diseases Societies. The European Journal of Public Health. 2015;25(1):9-14.

2. Jiang X, Jiang X, Liu Y, et al. Chemopreventive activity of sulforaphane. Drug design, development and therapy. 2018: 2905-13.

3. Cheung KL, Kong A-N. Molecular targets of dietary phenethyl isothiocyanate and sulforaphane for cancer chemoprevention. The AAPS journal. 2010; 12:87-97.

4. Akhlaghi M, Bandy B. Dietary broccoli sprouts protect against myocardial oxidative damage and cell death during ischemia-reperfusion. Plant Foods for Human Nutrition. 2010; 65:193-9.

5. Moon J-K, Kim J-R, Ahn Y-J, Shibamoto T. Analysis and anti-Helicobacter activity of sulforaphane and related compounds present in broccoli (Brassica oleracea L.) sprouts. Journal of Agricultural and Food Chemistry. 2010;58(11):6672-7.

6. Baenas N, Gómez-Jodar I, Moreno DA, García-Viguera C, Periago PM. Broccoli and radish sprouts are safe and rich in bioactive phytochemicals. Postharvest Biology and Technology. 2017; 127:60-7.

7. Le TN, Chiu C-H, Hsieh P-C. Bioactive compounds and bioactivities of Brassica oleracea L. var. italica sprouts and microgreens: An updated overview from a nutraceutical perspective. Plants. 2020;9(8):946.

8. Roussel P, Hernandez-Verdun D. Identification of Ag-NOR proteins, markers of proliferation related to ribosomal gene activity. Experimental cell research. 1994;214(2):465-72.

9. Nisari M, Eroz R, Ertekin T, et al. Investigation of argyrophilic nucleolar organizing region. BRATISLAVA MEDICAL JOURNAL-BRATISLAVSKE LEKARSKE LISTY. 2016;117(6).

10. Goodpasture C, Bloom SE. Visualization of nucleolar organizer regions in mammalian chromosomes using silver staining. Chromosoma. 1975;53(1):37-50.

11. Trere D. AgNOR staining and quantification. Micron. 2000;31(2):127-31.

12. Lindner LE. Improvements in the silver-staining technique for nucleolar organizer regions (AgNOR). Journal of Histochemistry & Cytochemistry. 1993;41(3):439-45.

13. Baykara O. Current Approaches in Cancer Treatment. Balikesir Journal of Health Sciences. 2016; 5(3): 154-165.

14. Ullah MF, Bhat SH, Husain E, et al. Cancer chemopreventive pharmacology of phytochemicals derived from plants of dietary and non-dietary origin: implication for alternative and complementary approaches. Phytochemistry Reviews. 2014; 13:811-33.

15. Abuajah CI, Ogbonna AC, Osuji CM. Functional components and medicinal properties of food: a review. Journal of food science and technology. 2015; 52:2522-9.

16. Ambrosone CB, McCann SE, Freudenheim JL, et al. Breast cancer risk in premenopausal women is inversely associated with consumption of broccoli, a source of isothiocyanates, but is not modified by GST genotype. The Journal of nutrition. 2004;134(5):1134-8.

17. Fimognari C, Hrelia P. Sulforaphane as a promising molecule for fighting cancer. Mutation Research/Reviews in Mutation Research. 2007;635(2-3):90-104.

18. López-Chillón MT, Carazo-Díaz C, Prieto-Merino D, et al. Effects of long-term consumption of broccoli sprouts on inflammatory markers in overweight subjects. Clinical Nutrition. 2019;38(2):745-52.

19. Mao F, Xiao B, Jiang Z, et al. J. Anticancer effect of Lycium barbarum polysaccharides on colon cancer cells involves G0/G1 phase arrest. Medical Oncology. 2011; 28:121-6.

20. Pham N-A, Jacobberger JW, Schimmer AD, et al. The dietary isothiocyanate sulforaphane targets pathways of apoptosis, cell cycle arrest, and oxidative stress in human pancreatic cancer cells and inhibits tumor growth in severe combined immunodeficient mice. Molecular cancer therapeutics. 2004;3(10):1239-48.

21. Cornblatt BS, Ye L, Dinkova-Kostova AT, et al. Preclinical and clinical evaluation of sulforaphane for chemoprevention in the breast. Carcinogenesis. 2007;28(7):1485-90.

22. Kallifatidis G, Rausch V, Baumann B, et al. Sulforaphane targets pancreatic tumour-initiating cells by NF-κB-induced antiapoptotic signalling. Gut. 2009;58(7):949-63.

23. Myzak MC, Dashwood RH. Chemoprotection by sulforaphane: keep one eye beyond Keap1. Cancer letters. 2006;233(2):208-18.

24. Licznerska B, Szaefer H, Matuszak I, Murias M, and Baer-Dubowska W. Modulating Potential of L-Sulforaphane in the Expression of Cytochrome P450 to Identify Potential Targets for Breast Cancer Chemoprevention and Therapy Using Breast Cell Lines. Phytotherapy Research. 2015;29(1):93-9.

25. Lewinska A, Adamczyk-Grochala J, Deregowska A, and Wnuk M. Sulforaphane-induced cell cycle arrest and senescence are accompanied by DNA hypomethylation and changes in microRNA profile in breast cancer cells. Theranostics. 2017;7(14):3461.

26. Licznerska B, Szaefer H, Krajka-Kuźniak V. R-sulforaphane modulates the expression profile of AhR, ERα, Nrf2, NQO1, and GSTP in human breast cell lines. Molecular and Cellular Biochemistry. 2021; 476:525-33.

27. Pledgie-Tracy A, Sobolewski MD, Davidson NE. Sulforaphane induces cell type–specific apoptosis in human breast cancer cell lines. Molecular cancer therapeutics. 2007;6(3):1013-21.

28. Paśko P, Tyszka-Czochara M, Galanty A, et al. Comparative study of predominant phytochemical compounds and proapoptotic potential of broccoli sprouts and florets. Plant Foods for Human Nutrition. 2018; 73:95-100.

29. Kim H-J, You M-K, Lee Y-H, et al. Red pepper seed water extract inhibits preadipocyte differentiation and induces mature adipocyte apoptosis in 3T3-L1 cells. Nutrition research and practice. 2018;12(6):494-502.

30. Lin HW, Hsieh MJ, Yeh CB, et al. Coronarin D induces apoptotic cell death through the JNK pathway in human hepatocellular carcinoma. Environmental toxicology. 2018;33(9):946-54.

31. Jackson SJ, Singletary KW. Sulforaphane: a naturally occurring mammary carcinoma mitotic inhibitor, which disrupts tubulin polymerization. Carcinogenesis. 2004;25(2):219-27.

32. Cheng A-C, Shen C-J, Hung C-M, et al. C. Sulforaphane decrease of SERTAD1 expression triggers G1/S arrest in breast cancer cells. Journal of medicinal food. 2019;22(5):444-50.

33. Rutz J, Juengel E, Euler S, et al. Chronic sulforaphane application does not induce resistance in renal cell carcinoma cells. Anticancer Research. 2018;38(11):6201-7.

34. Liu K-C, Shih T-Y, Kuo C-L, et al. Sulforaphane induces cell death through G2/M phase arrest and triggers apoptosis in HCT 116 human colon cancer cells. The American Journal of Chinese Medicine. 2016;44(06):1289-310.

35. Mao F, Xiao B, Jiang Z, Zhao J, Huang X, Guo J. Anticancer effect of Lycium barbarum polysaccharides on colon cancer cells involves G0/G1 phase arrest. Medical Oncology. 2011; 28:121-6.

36. Ertekin T, Bozkurt O, Eroz R, Nisari M, Bircan D, Nisari M, Unur E. May argyrophilic nucleolar organizing region–associated protein synthesis be used for selection of the most reliable dose of the drugs such as Rhamnetin in cancer treatments. Bratislava Medical Journal. 2016;117(11):653–658.

37. Nisari M, Eröz R. Does capsaicin have therapeutic benefits in human colon adenocarcinoma? Selection of the most reliable dose via AgNOR. Turkish Journal of Medical Sciences 2020; 50: 1076-1081.

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Is the serum uric acid (SUA) level and SUA/serum creatinine (Scr) ratio a predictive biomarker for microalbuminuria in patients with diabetes mellitus?

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ABSTRACT

The pathogenesis of diabetic nephropathy (DN) is very complex and is still not well understood. SUA has been associated with metabolic risk in a wide range of diseases. In this study, we aimed to investigate the effect of SUA and SUA/Scr ratio on renal function using glomerular filtration rate (GFR) and microalbuminuria.
A total of 399 patients with diabetes alone, excluding other conditions that affect uric acid levels, were included in the study. Patients were divided into normoalbuminuria (n:247) and microalbuminuria (n:152) groups. SUA, SUA/Scr ratios were compared.
Female gender was 53.4% in the normoalbuminuria group and 57.9% in the microalbuminuria group. There was no significant difference in gender between the groups. In the microalbuminuria group, SUA (p=0.032), glucose (p<0.001), GGT (p=0.003), HBA1C (p<0.001), and triglycerides (p<0.001) were significantly higher, while eGFR (p<0.005), HDL (p<0.001), and vitamin D (p=0.017) were significantly lower. There was a significant negative correlation between eGFR and SUA (p<0.001) and albuminuria (p=0.004) and a significant positive correlation between eGFR and SUA/Scr ratio (p<0.001).
Serum uric acid (SUA) levels have been found to be associated with renal function in diabetes. Our study confirms this association. The metabolic and microvascular effects of SUA are widely recognized. Nevertheless, further evidence is required to clarify the relationship between SUA/Scr ratio, which accounts for renal function, and DN

Keywords: Diabetic nephropathy, microalbuminuria, serum uric acid/creatine ratio

Diyabetes Mellitus hastalarında serum ürik asit (SUA) düzeyi ve SUA/Serum kreatin (Scr) oranı, mikroalbuminüri için prediktif bir belirteç olabilir mi?’

Süreç

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ÖZ

Diyabetik nefropatinin (DN) patogenezi çok karmaşıktır ve hala tam olarak anlaşılamamıştır. SUA birçok hastalıkta metabolik riskle ilişkili bulunmuştur. Bizde bu çalışmada SUA ve SUA/Scr oranının böbrek fonksiyonları üzerine etkisini glomeruler filtrasyon hızı (GFR) ve mikroalbüminüri ile araştırmayı amaçladık.
Çalışmaya sadece diyabeti olan, ürik asit düzeyini etkileyen diğer durumların dışlandığı toplam 399 hasta dahil edildi.Hastalar normoalbüminüri (n:247) ve mikroalbüminüri (n:152) grubu olarak ikiye ayrıldı. SUA, SUA/Scr oranları karşılaştırıldı.
Normoalbuminüri grubunda %53,4; mikroalbuminüri grubunda %57,9 kadın cinsiyet mevcuttu. Gruplar arasında cinsiyet açısından anlamlı farklılık yoktu. Mikroalbuminüri grubunda ürik asit (p=0,032), glukoz (p<0,001), GGT (p=0,003), HBA1C (p<0,001) ve trigliserid (p<0,001) düzeyleri anlamlı olarak yüksekti; eGFR (p<0,005), HDL (p<0,001) ve D vitamini (p=0,017)ise anlamlı olarak düşüktü. eGFR ile SUA (p<0,001) ve albuminüri ((p=0,004) arasında negatif yönlü SUA/Scr oranı(p<0,001) arasında ise pozitif yönlü anlamlı bir korelasyon izlendi.
SUA düzeyleri diyabette böbrek fonksiyonları ile ilişkili bulunmuştur. Çalışmamız bu görüşü desteklemektedir. SUA’in metabolik ve mikrovasküler etkileri iyi bilinmektedir. Ancak böbrek fonksiyonuna göre düzeltme yapan SUA/Scr oranı ile DN ilişkisini açıklayacak daha çok kanıta ihtiyaç vardır.

Anahtar sözcükler: Diyabetik nefropati, mikroalbünüri, serum ürik asit /creatin oranı

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Introduction

Diabetes Mellitus (DM) is a chronic disease with a rising occurrence caused by faults in insulin release and activity. According to 2019 data from the International Diabetes Federation, there are 463 million people with diabetes worldwide, and that number is expected to reach 700 million by 2045 [1]. The rising incidence of diabetes mellitus (DM) worldwide has a considerable effect on the healthcare system by augmenting workload and expenditures. Consequently, the battle against diabetes mellitus and its complications is of significant importance [2,3].

In addition to the treatment of hyperglycemia in diabetes, screening for complications, early diagnosis and interventions are very important in terms of preventing negative consequences and improving the patient's quality of life. Diabetic nephropathy (DN) is the most frequent microvascular complication in diabetes [4].

Given the rate of progression of end-stage renal failure requiring dialysis, diabetic nephropathy is a frequent complication that significantly diminishes the patient's quality of life and also causes substantial health expenses. DN develops in roughly one-third of patients with diabetes after a latent period of several years. The pathogenesis of DN is very complex and is still not well understood [5].

Diabetic nephropathy (DN) is a clinical condition that manifests as albuminuria, progressive reduction in glomerular filtration rate, and hypertension. Nevertheless, the indicator of established diabetic nephropathy is the presence of persistent albuminuria without any indication of concomitant retinopathy or other kidney disease 5.

The screening and diagnosis of DN still rely on albuminuria examination. Albuminuria is identified by a urinary albumin excretion rate ranging from 30-300 mg within 3 to 6 month intervals. To detect diabetic nephropathy in individuals diagnosed with type 2 diabetes, the American Diabetes Association recommends screening with microalbuminuria at the time of diagnosis and annually thereafter [5,6].

Serum uric acid is the end product of endogenous and exogenous purine metabolism. Elevated serum uric acid levels are associated with many diseases and have been linked to an increased risk of hypertension, chronic renal failure, diabetes, and cardiovascular disease. Endogenous fructose is produced through the polyol pathway in patients with diabetes. Increased fructose levels also contribute to fructose-mediated uric acid production. The relationship between high levels of SUA and the development of diabetic kidney disease has been suggested by several possible mechanisms. SUA is an inflammatory factor that may be a contributor to endothelial dysfunction. In addition, SUA stimulates vascular smooth muscle cell proliferation, angiotensin, and oxidative stress via the vascular renin-angiotensin system. According to animal studies, the fructose-uric acid axis may contribute to certain clinical manifestations of diabetic nephropathy in humans [1,7].

Several studies have demonstrated that hyperuricemia is an individual risk factor for DN. However, whether SUA is only a marker or a contributing factor for microvascular disease and nephropathy in patients with diabetes mellitus remains controversial [1].

Biomarkers are defined as characteristic factors that can be objectively measured and evaluated as indicators of normal physiological or pathological processes. A simple biomarker for diabetic nephropathy may allow for an early diagnosis of the disease. Early diagnosis and treatment will prevent progression and reduce mortality, morbidity and healthcare costs [8].

Recent studies have shown that SUA levels are an indicator of kidney damage in both diabetic and non-diabetic patients. High SUA levels have been associated with many diseases. However, the fact that SUA levels are affected by renal function is a limitation. Having standardized the degree of renal function, the search for a new biomarker that evaluates serum uric acid levels and reflects net uric acid production has begun. For this purpose, the SUA/Scr ratio was developed. Recent studies have reported that SUA/SCr is associated with metabolic changes or preserved renal function [9,10].

In our country and in many countries, the microalbuminuria level cannot be checked in primary care. However, measuring SUA and creatine levels, which are easier and more cost-effective tests, would lead to a more practical evaluation. Given the role of albuminuria in DN, which is more difficult and costly to assess, it is important to simply identify associated conditions when they cannot be studied as a test. In this study, we aimed to evaluate the relationship between SUA, SUA/SCr ratio, GFR and microalbuminuria in diabetic patients.

Material Method

The research protocol for this study was approved by the institutional review boards of XXX Provincial Health Directorate and XXX University of Health Sciences (approval number:2023/05-08, date: 25.04.2023)

The records of diabetic patients admitted to the Family Medicine Outpatient Clinic of our hospital were retrospectively analyzed. Patients over 18 years of age with type 1 and type 2 diabetes who had serum uric acid, creatine, eGFR values and albumin levels in spot urine were included in the study.

A spot urine albumin level ranging from 30 to 300 mg was classified as microalbuminuria 6.

Patients with conditions that affect serum uric acid levels and other nephropathy causes such as gout disease, hypertension diagnosis, history of malignancy, and receiving antihypertensive treatment were excluded from the study.

Statistical Analysis

SPSS version 26 (IBM®, Chicago, USA) was used for statistical analysis. Normal and abnormal distribution of the variables were analysed by Shapiro-Wilk test. Descriptive statistics were expressed as mean and standard deviation in numerical data showing normal distribution, median (minimum-maximum) in data showing abnormal distribution, number and percentage in nominal data. "Student's T-test" and "One-way ANOVA" were used to analyse numerical variables showing normal distribution, and "Mann-Whitney U" test was used to analyse variables not showing normal distribution. Nominal data were compared using "Chi-square analysis". A p value below 0.05 was considered significant in statistical analyses.

Results

A total of 399 patients were included in the study. Patients were divided into 2 groups according to albuminuria level. The mean age was 53.77±11.94 years in the normoalbuminuria group and 54.69±13.16 years in the microalbuminuria group. No significant difference was observed between the groups in terms of age. Female gender was 53.4% in the normoalbuminuria group and 57.9% in the microalbuminuria group. There was no significant difference between the groups in terms of gender. In the microalbuminuria group, uric acid ($p=0.032$), glucose ($p<0.001$), GGT ($p=0.003$), HBA1C ($p<0.001$) and triglyceride ($p<0.001$) levels were significantly higher; eGFR ($p<0.005$), HDL ($p<0.001$) and vitamin D ($p=0.017$) were significantly lower. There was no significant difference between the groups in terms of other laboratory parameters.

The distribution and analysis of demographic characteristics and laboratory parameters between the groups are summarised in Table 1.

In the correlation analysis, a significant negative correlation was found between age and SUA/Scr ratio ($p=0.003$) and eGFR ($p<0.001$). A significant negative correlation was observed between eGFR and uric acid ($p<0.001$) and albuminuria (($p=0.004$) and a significant positive correlation was observed between SUA/Scr ratio ($p<0.001$) (Table 2).

Table 1. Comparison of demographic characteristics and laboratory parameters between groups			
	Normoalbuminuria (N=247)	**Microalbuminuria (N=152)**	**p value**
Age*	53,77±11,94	54,69±13,16	0,357¥
Gender, Female***	132 (53,4)	88 (57,9)	0,385¥¥¥
Serum Uric acid (mg/dl)**	4,40 (1,5-33)	4,9 (1,5-12,1)	***0,032¥¥***
Serum Creatinine (µmol/L)**	0,89 (0,44-1,89)	0,89 (0,47-5,39)	0,280¥¥
SUA/Scr**	5,13 (1,9-45,21)	4,93 (0,04-16,38)	0,946¥¥
GFR (ml/dk/1,73m²)**	86 (19-132)	80 (8-144)	***0,005¥¥***
Glucose (mg/dl)**	151 (53-499)	177 (73-444)	***<0,001¥¥***
ALT (U/L)**	19 (5-137)	19 (8-335)	0,621¥¥
GGT (U/L)**	25 (7-351)	29 (11-306)	***0,003¥¥***
Hemoglobin (g/dl)**	14 (9-18,7)	14,1 (3,6-18,1)	0,386¥¥
HBA1C**	7,7 (5,1-15,7)	9 (5-15,2)	***<0,001¥¥***
Triglyceride (mg/dl)**	143 (22-565)	171 (37-734)	***<0,001¥¥***
HDL (mg/dl)**	47 (20-165)	42,5 (17-70)	***0,001¥¥***
LDL (mg/dl)**	117 (31-250)	122 (5-255)	0,575
Total cholesterol (mg/dl)**	195 (83-338)	201 (83-361)	0,390
Vitamin D (µg/L)**	14 (1-149)	11,91 (1,82-35)	***0,017¥¥***

*Mean±sd;**Median (min-max);***N(%).¥Independent Groups T Test; ¥¥Man Whitney U Test; ¥¥¥Ki-square test. SUA/Scr: Serum uric acid/Serum creatinine GFR: Glomerular Filtration Rate; ALT:Alanin Amino Transferaz; GGT: Gama Glutamil Transferaz;HBA1C: Hemoglobin A1C;HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein.

Table 2. Correlation analysis between age and other laboratory parameters					
		Age	**Uric acid**	**SUA/Scr**	**eGFR**
Uric acid*	rho	0,014	-		
	p	0,777	-		
SUA/Scr*	rho	-0,147	0,621	-	
	p	***0,003***	***<0,001***	-	
eGFR*	rho	-0,494	-0,351	0,249	-
	p	***<0,001***	***<0,001***	***<0,001***	-
Albuminüria*	rho	0,078	0,090	-0,031	-0,146
	p	0,120	0,073	0,541	***0,004***

Discussion

Diabetic nephropathy is one of the leading causes of end-stage renal disease worldwide. Many studies have been conducted on the prevention and treatment of this important complication of diabetes. Considering the rising prevalence of DN, the present screening methods or tests for determining DN risk seem deficient. It is also important to introduce new biomarkers other than eGFR and microalbuminuria. In our study, we found a significant negative correlation between eGFR and uric acid and albuminuria, and a significant positive correlation with the SUA/Scr ratio. We also found that SUA level was significantly higher in the microalbuminuric patient group. There are many studies showing the association of SUA with diabetic kidney disease 1,11-13. However, studies investigating the SUA/Scr ratio are limited 14. Again, SUA levels have mostly been compared with eGFR levels, and there are relatively few studies with albuminuria 15-17.

Hyperuricemia is associated with worsening eGFR, albuminuria, chronic kidney disease and renal failure, according to Sharma's meta-analysis. PMID: 34104231. Hovind et al. also found that high normal SUA levels were associated with the incidence of diabetic renal failure in 277 newly diagnosed type 1 DM patients 18.

In contrast, Hayashino et al. found no association between SUA levels and eGFR decline or development of albuminuria, probably due to the heterogeneity of baseline eGFR and the short follow-up period of 1.8 years 19.

Two studies were found in the literature which evaluated the SUA/Scr ratio and the renal function in diabetic patients. Among these, Kawamato et al. used eGFR as an indicator of renal function and showed that the SUA/Scr ratio at baseline was independently and significantly associated with future decline in renal function 14.

The second study was conducted by Chen et al. In this retrospective study, SUA/Scr was found to be an independent risk factor for diabetic kidney disease in patients with type 2 diabetes, and it was emphasised that it may be helpful in detecting normoalbuminuric diabetic kidney disease 20.

In our study, we found a significant correlation between the SUA/Scr ratio and the eGFR, but not between the SUA/Scr ratio and microalbuminuria. This suggests that the metabolic effects of SUA levels may be influenced by different parameters after adjustment for renal function.

Decreases in eGFR without albuminuria are often reported in patients with diabetes. In a study by Qin et al, high SUA was shown to reduce eGFR even in people with diabetes without albuminuria 21,22. In our study, we did not find an association between microalbuminuria and SUA level and SUA/Scr ratio, but we did find a significant association with eGFR. This is in support of the study by Qin et al. However, the different results suggest that more research is needed on this topic.

Limitations:

Although this study only included a sample group with diabetes and excluded other comorbidities that may affect renal function, we had important limitations. Firstly, the retrospective nature of the study, the relatively small number of the microalbuminuria group and the use of spot urine examination for the evaluation of microalbuminuria can be counted as important limitations.

Conclusion

Considering the metabolic effects of SUA and especially its microvascular effects, we think that its effect on the complications of diabetes should be examined in more detail. The presence of studies suggesting that only strict glycaemic control is not sufficient in the progression of diabetes and development of complications supports our opinion 23. SUA/Scr ratio may be a more valuable biomarker that corrects for renal function. However, studies in DN are insufficient. We think that prospective larger scale studies are needed.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interst with respect to the research, authorship, and/or puplication of this article.

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References

1. Ji P, Zhu J, Feng J, et al. Serum uric acid levels and diabetic kidney disease in patients with type 2 diabetes mellitus: A dose-response meta-analysis. Primary care diabetes. 2022;16(3):457-465.
2. Jing Z, Chu J, Imam Syeda Z, et al. Catastrophic health expenditure among type 2 diabetes mellitus patients: A province-wide study in Shandong, China. Journal of diabetes investigation. 2019;10(2):283-289.
3. Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. PloS one. 2018;13(3):e0194127.
4. Long AN, Dagogo-Jack S. Comorbidities of diabetes and hypertension: mechanisms and approach to target organ protection. Journal of clinical hypertension (Greenwich, Conn). 2011;13(4):244-251.
5. Samsu N. Diabetic Nephropathy: Challenges in Pathogenesis, Diagnosis, and Treatment. BioMed research international. 2021;2021:1497449.
6. Sternlicht H, Bakris GL. Management of Hypertension in Diabetic Nephropathy: How Low Should We Go? Blood purification. 2016;41(1-3):139-143.
7. Bjornstad P, Lanaspa MA, Ishimoto T, et al. Fructose and uric acid in diabetic nephropathy. Diabetologia. 2015;58(9):1993-2002.
8. Thipsawat S. Early detection of diabetic nephropathy in patient with type 2 diabetes mellitus: A review of the literature. Diabetes & vascular disease research. 2021;18(6):14791641211058856.
9. Al-Daghri NM, Al-Attas OS, Wani K, Sabico S, Alokail MS. Serum Uric Acid to Creatinine Ratio and Risk of Metabolic Syndrome in Saudi Type 2 Diabetic Patients. Scientific reports. 2017;7(1):12104.
10. Gu L, Huang L, Wu H, Lou Q, Bian R. Serum uric acid to creatinine ratio: A predictor of incident chronic kidney disease in type 2 diabetes mellitus patients with preserved kidney function. Diabetes & vascular disease research. 2017;14(3):221-225.
11. Katsiki N, Dimitriadis GD, Mikhailidis DP. Serum Uric Acid and Diabetes: From Pathophysiology to Cardiovascular Disease. Current pharmaceutical design. 2021;27(16):1941-1951.
12. Mauer M, Doria A. Uric acid and risk of diabetic kidney disease. Journal of nephrology. 2020;33(5):995-999.
13. Liu L, Gao B, Wang J, et al. Time-averaged serum uric acid and 10-year incident diabetic kidney disease: A prospective study from China. Journal of diabetes. 2020;12(2):169-178.
14. Kawamoto R, Ninomiya D, Kikuchi A, et al. Serum uric acid to creatinine ratio is a useful predictor of renal dysfunction among diabetic persons. Diabetes & metabolic syndrome. 2019;13(3):1851-1856.
15. Yan D, Tu Y, Jiang F, et al. Uric Acid is independently associated with diabetic kidney disease: a cross-sectional study in a Chinese population. PloS one. 2015;10(6):e0129797.
16. Zhu L, Sun J, Wang X, et al. Elevated serum uric acid is not an independent risk factor for the occurrence of Type 2 diabetic kidney disease in Chinese populations. Medicine. 2022;101(50):e32128.
17. Kocak MZ, Aktas G, Duman TT, Atak BM, Savli H. Is Uric Acid elevation a random finding or a causative agent of diabetic nephropathy? Revista da Associacao Medica Brasileira (1992). 2019;65(9):1155-1160.
18. Hovind P, Rossing P, Tarnow L, Johnson RJ, Parving HH. Serum uric acid as a predictor for development of diabetic nephropathy in type 1 diabetes: an inception cohort study. Diabetes. 2009;58(7):1668-1671.
19. Hayashino Y, Okamura S, Tsujii S, Ishii H. Association of serum uric acid levels with the risk of development or progression of albuminuria among Japanese patients with type 2 diabetes: a prospective cohort study [Diabetes Distress and Care Registry at Tenri (DDCRT 10)]. Acta diabetologica. 2016;53(4):599-607.
20. Chen L, Zhu Z, Ye S, Zheng M. The Serum Uric Acid to Serum Creatinine Ratio is an Independent Risk Factor for Diabetic Kidney Disease. Diabetes, metabolic syndrome and obesity : targets and therapy. 2022;15:3693-3703.

21. Qin Q, Qian Y, Zhu G, Fan W, Niu J, Gu Y. The Correlation between Serum Uric Acid and Renal Function in Elderly Chinese Diabetes with Normoalbuminuria. International journal of endocrinology. 2019;2019:1435875.
22. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2021. Diabetes care. 2021;44(Suppl 1):S151-s167.
23. Tanaka K, Hara S, Hattori M, et al. Role of elevated serum uric acid levels at the onset of overt nephropathy in the risk for renal function decline in patients with type 2 diabetes. Journal of diabetes investigation. 2015;6(1):98-104.

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Clinical Features of Drug Hypersensitivity and Factors Affecting Drug-Induced Anaphylaxis: Single Center Experience of the Tertiary University Hospital

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Research Article

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ABSTRACT

Background-Aims: The prevalence and incidence of drug-induced hypersensitivity reactions (HSRs) are increasing worldwide. They are causing increasing morbidity and costs. Also, for physicians, they are one of the most challenging issues to manage. Understanding the etiology, prevalence, and triggering factors of drug-induced HSRs to treat and prevent them is important. Some literature data have shown the frequency of DHR to be approximately 2% in our country, however, to date, the eastern part of Central Anatolia has not been investigated for drug-induced HSRs particularly. In line with all this information, we aim to determine the frequency, etiology, and clinical features of drug hypersensitivity reactions (DHRs), and to evaluate the factors affecting drug-induced anaphylaxis among the patients admitted to the outpatient allergy clinic of the tertiary university hospital.

Materials-methods: In this retrospective cohort study, medical records of the 8295 patients who visited the allergy outpatient clinic of Sivas Cumhuriyet University Hospital from 2nd July 2018 to 10 December 2019 were retrospectively reviewed by the hospital data system using the ICD-code Y57.4 (adverse effects caused by pharmacological agents). The frequency, etiologies, demographic, and clinical features of the DHRs were evaluated.

Results: Among the 8295 patients who visited the allergy outpatient clinic of Sivas Cumhuriyet University Hospital, 159 patients with a mean age of 40,52± 14,85 years (129 female, 30 male) were evaluated with the diagnosis of DHRs. The frequency of DHRs among admissions was found to be approximately 2%. Accompanying allergic diseases included respiratory (17%), cutaneous (10%), venom (n=3), drug (7%), and food hypersensitivity (n=2). Multiple allergic diseases were detected in 20%. Eighty-six % (n=138) could recognize the culprit drug. The causes of drug hypersensitivity were non-steroidal anti-inflammatory drugs (NSAIDs) (27%), beta-lactams (16%), co-sensitization to beta-lactams and NSAIDs (8%), non-beta lactam antibiotics (8%), and other kinds of drugs (39%). Type 1 reaction occurred in 80%, type 4 in 21%, non-immune mediated in 7, and mixed type composed of type 1 and 4 in 9 patients. Anaphylaxis occurred in 46,5%. Fifteen% had grade 2, 22% had grade 3, and 4 had grade 4 anaphylactic reactions. Systematical assessment showed cutaneous symptoms in 93%, respiratory in 38%, cardiovascular in 29.5%, neurologic in 25%, and gastrointestinal in 11%. Allergy to NSAIDs (88,6 %) and beta-lactams (82,5%) were more frequent in type 1 reactions than in type 4 and mixed type reactions (p<0,001).

Discussion-conclusions: Drug-induced anaphylaxis was commonly grade 3, occurred by NSAIDs and beta-lactams, and presented with cutaneous symptoms. Although drug-induced HSRs generally occurred by NSAIDs and/or beta-lactams, drugs such as proton pump inhibitors and vitamins were the culprits in up to 40% of the cases. Particular attention should be paid to this group in the evaluation of drug-induced anaphylaxis. Healthcare providers and patients need to be informed more to avoid neglecting the diagnosis of DHRs, especially drug-induced anaphylaxis.

Keywords: Drug hypersensitivity, frequency, anaphylaxis, hypersensitivity reactions

İlaç Aşırı Duyarlılığının Klinik Özellikleri ve İlaç ile İndüklenen Anafilaksiyi Etkileyen Faktörler: Üçüncü Basamak Üniversite Hastanesi Tek Merkez Deneyimi

Süreç

Geliş: 14/08/2023
Kabul: 25/09/2023

ÖZ

Giriş- amaç: İlaca bağlı aşırı duyarlılık reaksiyonlarının (ADR) prevalansı ve insidansı dünya çapında artmaktadır. Artan morbiditeye ve maliyetlere neden oluyorlar. Ayrıca hekimler için yönetilmesi en zor konulardan biridir. İlaca bağlı HSR'lerin etiyolojisini, yaygınlığını ve tetikleyici faktörlerini anlamak, bunları tedavi etmek ve önlemek önemlidir. Bazı literatür verileri ülkemizde DHR sıklığının yaklaşık %2 olduğunu göstermektedir ancak bugüne kadar Orta Anadolu'nun doğu kısmı uyuşturucuya bağlı HSR açısından özellikle araştırılmamıştır. Bütün bu bilgiler doğrultusunda amacımız, üçüncü basamak bir üniversite hastanesi alerji polikliniğine başvuran hastalarda ilaç aşırı duyarlılığının sıklığını, etiyolojisini ve klinik özelliklerini belirlemek ve ilaç ile indüklenen anafilaksiyi etkileyen faktörleri değerlendirmektir.

Materyal-metodlar: Bu retrospektif kohort çalışmasında, Sivas Cumhuriyet Üniversitesi Hastanesi alerji polikliniğine 2 Temmuz 2018 - 10 Aralık 2019 tarihleri arasında başvuran 8295 hastanın tıbbi kayıtları geriye dönük olarak hastane veri sistemi tarafından ICD kodu Y57.4 (farmakolojik ajanların neden olduğu advers etkiler) kullanılarak incelendi. İlaç aşırı duyarlılık reaksiyonlarının (ADR) sıklığı, etiyolojileri, demografik ve klinik özellikleri değerlendirildi.

Bulgular: Sivas Cumhuriyet Üniversitesi Hastanesi alerji polikliniğine başvuran 8295 hastadan yaş ortalaması 40,52± 14,85 olan 159 hasta (129 kadın, 30 erkek) ilaç ile indüklenen aşırı duyarlılık reaksiyonu (İAR) tanısı ile değerlendirildi. Başvurular arasında IAR sıklığı yaklaşık %2 saptanmıştır. Eşlik eden alerjik hastalıklar arasında solunum (%17), deri (%10), venom (n=3), ilaç (%7) ve gıda (n=2) aşırı duyarlılığı yer almıştır. Çoklu alerjik hastalık tanısı %20'sinde saptandı. %86'sı (n=138) sorumlu ilacı tanıyabildi. İlaç alerjisinin nedenleri non-steroid anti-inflamatuar ilaçlar (NSAII'ler) (%27), beta-laktam antibiyotikler (%16), beta-laktamlara ve NSAII'lere eş zamanlı duyarlılık varlığı (%8), non-beta laktam antibiyotikler (%8) ve diğer tür ilaçlardı (%39). Hastaların %80'inde tip 1, %21'inde tip 4, 7'sinde non-immun aracılı ve 9'unda tip 1 ve 4'ten oluşan mikst tip reaksiyon görüldü. Anafilaksi %46,5 oranında meydana geldi. %15'inde derece 2, %22'sinde derece 3 ve 4'ünde derece 4 anafilaktik reaksiyon vardı. Sistematik değerlendirmeye göre %93 deri, %38 solunum, %29,5 kardiyovasküler, %25 nörolojik ve %11 gastrointestinal semptomlar gözlendi. NSAII'lere (% 88,6) ve beta-laktamlara (% 82,5) alerji, tip 1 reaksiyonlarda, tip 4 ve karma tip reaksiyonlara göre daha sıktı (p<0,001).

Tartışma ve sonuçlar: İlaç ile indüklenen anafilaksi genellikle 3. Derece idi, NSAII'ler ve beta-laktamlar tarafından meydana geliyordu ve kutanöz semptomlarla kendini göstermekteydi. İlaç ile indüklenen ADR'ler genellikle NSAII ve/veya beta-laktamlar tarafından meydana gelse de, vakaların %40'e varan kısmında proton pompası inhibitörleri ve vitaminler gibi ilaçlar suçludur. İlaç ile indüklenen anafilaksinin değerlendirilmesinde bu gruba özel dikkat gösterilmelidir. Özellikle ilaç ile indüklenen anafilaksi başta olmak üzere İAR tanısının ihmal edilmemesi için sağlık çalışanlarının ve hastaların daha fazla bilgilendirilmesi gerekmektedir.

Anahtar sözcükler*:* İlaç aşırı duyarlılığı, sıklık, anafilaksi, aşırı duyarlılık reaksiyonları

License

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Introduction

Drug hypersensitivity reactions usually develop unexpectedly and unpredictably with the use of drugs at normal therapeutic doses and are called adverse drug reactions. These reactions may develop non-immunologically (pseudoallergic/intolerance) or immunologically. True allergic (immunological) reactions are divided into early and late types; and are mediated by IgE and T cells, respectively. While conditions such as urticaria, angioedema, and anaphylaxis occur after contact with the drug and are included in the early-type drug hypersensitivity group; dermatitis, maculopapular exanthema, and severe cutaneous drug reactions are included in the delayed-type drug hypersensitivity reaction group [1].

Immunological drug hypersensitivity reactions should be diagnosed and treated promptly. For allergists and other physicians, drug allergies are one of the most difficult issues to manage in daily practice [2,3].

The prevalence and incidence of drug-induced hypersensitivity reactions are increasing worldwide. Drug-induced adverse reactions are among the important causes of increased morbidity and cost in hospitalized patients [2,3].

It is important to understand the etiology, prevalence, and triggering factors of drug-induced hypersensitivity reactions, to treat these patients correctly, prevent the recurrence of drug-induced hypersensitivity reactions, and develop prevention methods [1-3].

In various studies conducted in our country, the prevalence of self-reported DHR varies between 2.9% and 4.7% in students and adult male groups [4-6].

In addition, DHR frequency among outpatient clinic admissions was shown to be approximately 2% in a national multicenter study [7], but the northeast of our country was not examined on a regional basis. In particular, it is important to determine the frequency of drug hypersensitivity reactions seen in patients who applied to the allergy and clinical immunology outpatient clinic in Sivas province and to define the demographic and clinical characteristics of these patients, as they reflect the eastern part of Central Anatolia in Turkey.

In line with all this information, we aimed to investigate the frequency, the etiologies, the diversity of clinical presentations, the risk factors, and the treatments applied to the cases with DHRs admitted to the Cumhuriyet University Medical Faculty Hospital, Department of Chest Diseases, Allergy and Clinical Immunology outpatient clinics.

Material Method

The medical records of 8295 patients over the age of 16 who applied to the outpatient clinic of Sivas Cumhuriyet University Faculty of Medicine, Department of Chest Diseases, Division of Allergy and Clinical Immunology, between 2 July 2018 and 10 December 2019 due to DHRs were analyzed cross-sectionally and retrospectively through the hospital data system. 159 cases with Y57.4 ICD code (adverse effects caused by pharmacological agents) entry were included in our study.

At first, the frequency of DHRs among the admitted patients was evaluated, and then the history of drug reactions and demographic data were recorded using a detailed questionnaire. The patients' gender, age, presence of atopic disease, existing chronic diseases, drugs they use constantly, clinical features of DHRs (organ systems affected), culprit drug/drugs, the treatments applied in the case of DHRs, along with case report forms, were cross-sectionally and retrospectively obtained from hospital records.

DHRs are classified as immediate-type (urticaria, angioedema, bronchospasm, laryngeal edema, rhinitis, hypotension, and allergic shock) and delayed-type (maculopapular reactions and DRESS- Drug Reaction with Eosinophilia and Systemic Symptoms, fixed drug eruption,s contact dermatitis, vasculitic reactions, photosensitivity, as well as severe cutaneous drug reactions; Steven-Johnson syndrome, acute generalized exanthematous pustulosis, and toxic epidermal necrolysis) [1]. Drug-induced anaphylaxis was categorized into 4 grades according to the Mueller classification [8].

According to the Mueller classification of anaphylaxis; Grade 1 HSR defines mild skin reactions (such as urticaria, pruritus, malaise, and anxiety), grade 2; general systemic reactions (urticaria, itching, and anxiety, as well as generalized edema, chest pressure, wheezing, abdominal pain, nausea-vomiting, and dizziness), grade 3; severe systemic reactions (in addition to those listed previously, dyspnea, dysphagia, deepening of the voice and difficulty in speech, and confusion), and grade 4 defines allergic shock (in addition to those listed previously, drop in blood pressure, collapse, incontinence, loss of consciousness).

The atopic status of the patients was analyzed to investigate the presence of allergic diseases among the cohort with drug hypersensitivity and to compare the presence of atopy with the types of drug allergy. The atopic status of our cases was evaluated by quantitative skin tests. Skin tests were performed with ALK Alutard® allergen extracts, including inhalant, food, venom, and latex allergens. Histamine was used as a positive control, and normal saline was used as a negative control. Since it is not available in our laboratory, allergen-specific IgE values could not be evaluated.

After the evaluation of the atopic status of the patients, they are categorized into two main groups according to having only one type of allergic disease (for example, only respiratory/ cutaneous/ food/ venom/ drugs) and having≥2 types of allergic disease at the same time (for example, to have co-sensitivity to venom together with food at the same time, etc.)

Based on ENDA's recommendations, the cases were managed [9]; diagnostic drug tests could not be performed because the conditions could not be met, but oral drug provocation tests were performed with appropriate alternative drugs for the necessary patients.

Statistical Analysis

Statistical Analyses Values were expressed as frequency (number and percentage), and mean (range) as appropriate. Fisher's exact test and chi-square tests were used for 2 × 2 comparisons of categorical variables. Mann-Whitney U and KruskalWallis H test was used to compare numerical variables, where the numbers were <30. Statistical analyses were performed using the SPSS software package, version 23 (SPSS Inc., Chicago, IL, USA). Results with $p<0.05$ were evaluated as statistically significant.

Ethical Approval

Our study was approved by Sivas Cumhuriyet University, non-interventional clinical research ethics committee with the decision number 2020-01/01 dated January 15, 2020.

Results

1. Study Group and the Frequency of DHRs

Y57.4 ICD code (adverse effects caused by pharmacological agents) entry was detected in 159 cases out of 8295 applications during our study period, and the frequency of DHRs among allergy outpatient applications was found to be 2%.

2. Demographics and Characteristics of the Patients with DHRs

A total of 159 patients with a mean age of 40,52± 14,85 years (129 female, 30 male) were evaluated. Ninety- two (57%,n=92) had atopic diseases. Single-type allergic diseases included venom (n=3), drug (n=12), food (n=2), respiratory (n=27), and cutaneous allergies (n=16). Multiple allergic diseases were detected in 32 (20%) (*Figure 1*).

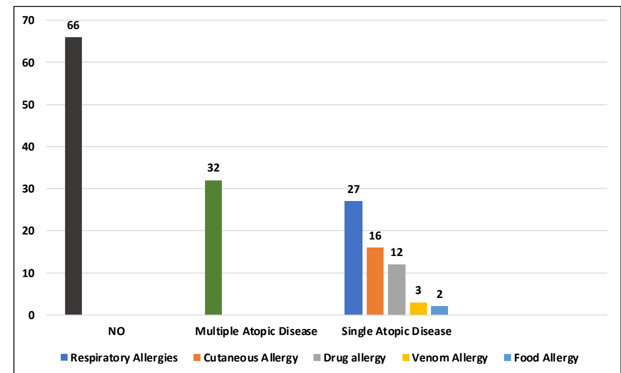

Figure 1. *Distribution of atopic diseases among patients with DHRs (shown as numbers)*

Ninety-three (58%, n=93) had a history of chronic diseases; of them, 13 had autoimmune diseases, and 7 had autoinflammatory diseases (8% and 4%, respectively). Seventy (44%) had chronic drug usage, and of them, 23 used anti-hypertensive drugs (%14) (Table 1).

Prick tests were assessed in 85 patients, of them 64 resulted negative. Twelve (n=12) had inhalant allergen sensitivity. Pollen and cockroach/house dust mite sensitivity were observed equally. 8 had polysensitization and only 1 had food sensitivity (*Figure 2*).

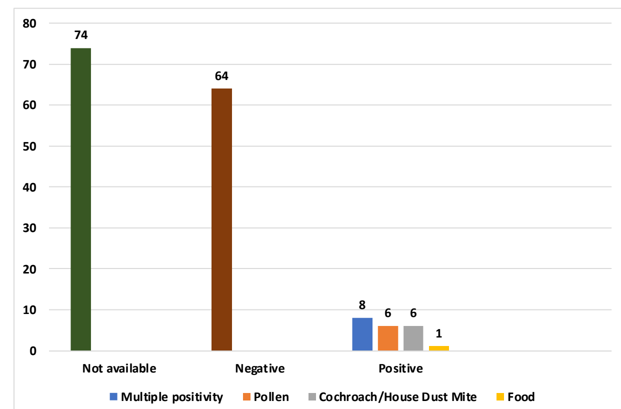

Figure 2. *Prick test results of the patients with DHRs (shown as numbers)*

Table 1. General characteristics of patients with DHRs

Variable	Number, %
Total number of patients	159
Age, mean±SD (years)	40,52± 14,85
Gender (female/male)	129/30
Chronic disease	93 (58%)
Chronic drug usage	70 (44%)
Anti-hypertensive drug usage	23 (14%)
Atopic disease	92 (57%)
Autoimmune disease	13 (8%)
Autoinflammatory disease	7 (4%)

3. Characteristics of the DHRs

Among 159, 138 (86%) could recognize the culprit drug (Table 2). The causes of drug hypersensitivity reactions were NSAIDs (n=44, 27%), beta-lactams (n=26, 16%), co-sensitization to beta-lactams and NSAIDs (n=14, 8%), antibiotics/ non-beta lactam antibiotics (n=13, 8%), and the other drugs (local and general anesthetics, proton pump inhibitors, vitamins, oral iron replacement therapy, disease-modifying anti-rheumatic drugs- DMARDs, antilipidemic, oral antimuscarinics, diuretics, oral anti-emetics, ACEI/ARBs, radiocontrast agents, antihistaminics, and oral anti-diabetics) (n=62, 39%) (*Figure 3*). In 127 (80%) of the DHRs, patients received the culprit drugs perorally.

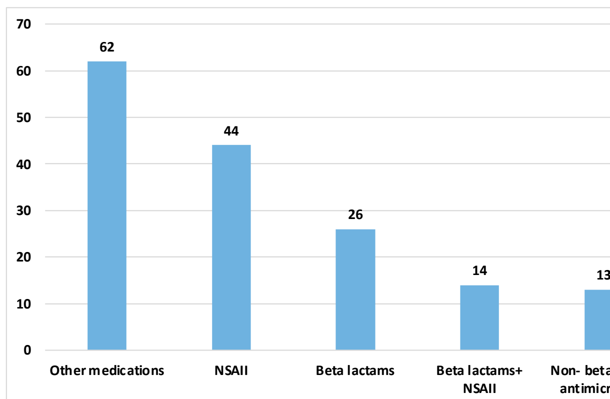

Figure 3. *The etiologies of DHRs (The frequencies of the culprit drugs are given as numbers).*

Type 1 reaction occurred in 116 (72%), type 4 occurred in 34 (21%), non-immune mediated occurred in 7, and mixed type composed of type 1 and 4 occurred in 9 patients. Among the drug-allergic patients, anaphylaxis occurred in 74 (46,5%). Among them, 24 (15%) had grade 2, 36 (22%) had grade 3, and 4 had grade 4 anaphylactic reactions (*Figure 4*).

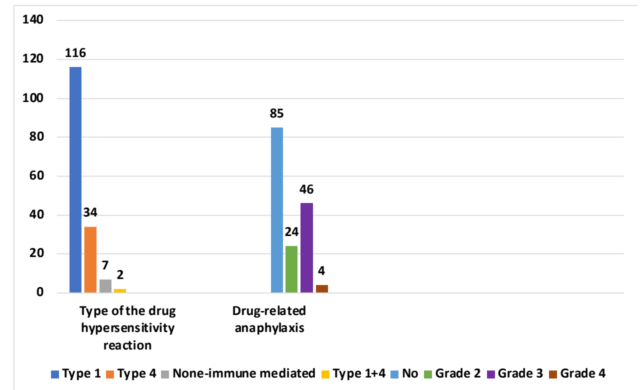

Figure 4. *Types of the DHRs and the distribution of the drug-induced anaphylaxis among our cohort (The frequencies are given as numbers).*

According to systematical assessment, cutaneous symptoms were observed in 148 (93%), respiratory in 61 (38%), cardiovascular in 47 (30%), neurological in 40 (25%), and gastrointestinal in 18 (11%) of all the patients (Table 2).

Table 2. Clinical characteristics and the treatment methods of DHR

Variable	**Number, %**
Recognition of the culprit drug	138 (86%)
Way of drug administration (po/pe)	127/32 (80%/20%)
Symptoms according to systematical assessment	
Mucocutaneous symptoms	148 (93%)
Respiratory symptoms	61 (38%)
Cardiovascular symptoms	47 (30%)
Neurological symptoms	40 (25%)
Gastrointestinal symptoms	18 (11%)
Hospitalization	8 (5%)
Drug-induced anaphylaxis	74 (46%)
Adrenalin administration	32 (20%)
Antihistaminic administration	153 (96%)
Corticosteroid administration	132 (83%)

(Abbreviations, po; peroral, pe; parenteral)

The local anesthetics and radiocontrast media drug skin tests were evaluated (n=17 and 7, respectively). The prick and intradermal tests were evaluated in line with the drug allergy guidelines (prick tests with the full concentration of the drug itself, and intradermal tests with the 1/100 and 1/10 dilutions of the drug, respectively). Histamine was used as positive and normal saline was used as negative controls. All of the drug skin tests with the local anesthetics and radiocontrast media resulted in negative.

When comparing the causes of drug hypersensitivity reactions with the atopic status; in the presence of concomitant atopic disease, beta-lactam sensitivity is observed and in the absence of atopic disease, sensitivity to antibiotics/ non-beta lactam antibiotics was observed (p=0,019) (Table 3).

When comparing the causes of drug allergy with the type of drug hypersensitivity, allergy to NSAIDs (88,5 %) and beta-lactams (82,5%) are more frequent in type 1 reactions than in type 4/mixed-type reactions (p<0,001) (Table 3).

While 100% of grade 4 anaphylactic reactions were observed within the first hour and grade 3 reactions were frequently within the first hour, the reactions that occurred after the 24th hour were completely grade 2 (p=0,043) (Table 3).

According to the systematical assessment, in the presence of beta-lactam allergy, respiratory symptoms were observed more frequently than the other types of drugs (p=0,018) (Table 3).

Table 3. The distribution of the frequencies according to the presence of atopic diseases, DHR types and grades, and the DHR-related symptoms is shown as based on the types of the culprit drugs.

Variables (n=159)	Atopic disease (+) (n=92)	Atopic disease (-) (n=67)		*P*
Beta-lactam allergy (n=40)	**77,5% (n= 31)**	22,5% (n=9)		0,019
Non-beta lactam antibiotics allergy (n=13)	38,5% (n=5)	**61,5% (n=8)**		
	Type 1 reactions (n=116)	**Type 4 reactions (n=34)**	**Mixed (Type 1+4) reactions (n=9)**	
NSAIDs allergy (n=44)	**88,5% (n=39)**	11,5% (n=5)	0	<0,001
Beta-lactam allergy (n=40)	**82,5% (n=33)**	17,5% (n=7)	0	
None-beta lactam antibiotics allergy (n=13) (n=13)	54% (n=7)	**46% (n=6)**	0	<0,05
Other kinds of drugs allergy (n=62)	60% (n=37)	25% (n=16)	**15% (n=9)**	
	Grade 2 (n=24)	**Grade 3 (n=46)**	**Grade 4 (n=4)**	
<1 hour (n=63)	27% (n=17)	66,7% (n=42)	**6,3% (n=4)**	0,043
1-24. hour (n=7)	43% (n=3)	57% (n=4)	0	
>24 hour (n=4)	**100% (n=4)**	0	0	
	Respiratory symptoms (+) (n=61)	**Respiratory symptoms (-) (n=98)**		
NSAIDs (n=44)	32% (n=14)	**68% (n=30)**		0,018
Beta-lactam antibiotics (n=40)	**58% (n=23)**	42% (n=17)		
None-beta lactam antibiotics (n=13)	15% (n=2)	**85% (n=11)**		
Other drugs (n=62)	36% (n=22)	**64% (n:40)**		

4. Management of the DHRs

Adrenalin injection was administered to 43% of the drug-induced anaphylaxis patients. These patients applied to emergency clinics and family practitioners to have the first step treatments of the drug HSRs. Especially, it is striking that only 43% of the anaphylaxis cases were treated with epinephrine administration. They were treated with antihistaminics and corticosteroid administrations. This result indirectly shows that the training of healthcare providers on the treatment of anaphylaxis is lacking.

Only 8 patients were hospitalized due to drug-induced anaphylaxis. As we observe in daily practice, antihistamines, and systemic corticosteroids (96% and 83%, respectively) were frequently administered in the case of drug hypersensitivity, with or without anaphylaxis (Table 2).

Discussion

In our study, drug hypersensitivity and drug-induced anaphylaxis cases admitted to the tertiary university hospital allergy outpatients in the north-

east of Turkey were analyzed retrospectively and the frequency was determined among applications from a single center. Our study did not include drug-induced adverse reactions, thus focusing on actual DHRs.

In the multicenter study of Çelik et al. in 2009-2010, the frequency of drug hypersensitivity was also found to be 2% in correlation with our study result [7]. Similar to the results by Çelik et al. from 11 centers across the country, the majority of the cases in which DHR was detected in our cohort were women, and respiratory and skin allergies or a combination of these accompanied the cases [7].

Consistent with the literature, NSAIDs were taken as the first-place culprits, followed by beta-lactams. In addition, immediate and grade 1 reactions (Mueller classification of anaphylaxis) are the most common and present with skin involvement. Non-immediate DHRs were relatively rare [10-12].

More than half of the cases had chronic systemic and/or accompanying atopic disease. The majority experienced DHRs on peroral treatments, with 46% describing drug-induced anaphylaxis, but <50% of them were administered adrenaline injections.

The lack of knowledge of physicians and health care providers, including allergists, in recognizing and treating anaphylaxis, prejudice about the side effects of adrenaline, and the presence of fear can be counted as the leading factors in the low rate of administration of adrenaline [13].

Besides, in general, while mucocutaneous manifestations are common, cardiovascular and neurologic symptoms are more common in grade 4 anaphylaxis. Although skin findings are frequently seen in the literature, consistent with our results, it should be kept in mind that anaphylaxis can occur without skin findings and even without cardiovascular collapse. In the absence of skin findings, the diagnosis of anaphylaxis becomes difficult, and the rate of adrenaline administration decreases in the absence of cardiovascular [13].

The diagnosis of anaphylaxis is mainly clinical. The most important point in diagnosis is awareness in primary care referral units. The first-line treatment for anaphylaxis is intramuscular (IM) adrenaline and it has no harm in anaphylaxis. Adrenaline administration also prevents prolonged and biphasic reactions.

In the event of an acute allergic reaction, the triggering agent should be removed first and then IM adrenaline should be administered by the caregivers and/or healthcare professionals. After this step, help should be called and the patient should lie flat and his/her feet should be lifted into the air. The required dose of adrenaline is 0.15 mg IM for children (<30 kg); and 0.3 mg IM for children (>30 kg) and adults. If necessary, IM adrenaline administration can be repeated at 5-10 minute intervals until help arrives [13].

After adrenaline administration, the patient should be monitored for vital signs. Vascular access should be established, intravenous fluid support (500-1000 cc bolus for adults, 10 mg/kg bolus for children and continued as needed), O2, inhaled B2 agonist, glucocorticoids and antihistaminics treatment should be applied when necessary [13].

As shown in our study, glucocorticoids and antihistaminics, which should be administered in the last step of the treatment of anaphylaxis, are applied in the first step with a frequency of almost 100%.

In addition, antihistaminics may not have life-saving effects but may have adverse cardiovascular effects (such as hypotension). They only have positive effects on cutaneous system findings.

Glucocorticoids are effective in preventing protracted signs and biphasic reactions. Their acute activities are limited, their effects begin later than adrenaline, and they have less positive cardiovascular effects. It should be kept in mind that they will have positive effects in the long-term treatments of anaphylaxis.

Cases known to be at risk (venom, food or drug allergies, etc.) should carry at least 2 adrenaline auto-injectors. Adrenaline auto-injector is the most important savior from fatal reactions, which should be preferred for long-term prophylaxis in these cases. Individualized treatment plans should be made for patients. Group activities can also eliminate judgments such as adrenaline side effects and fear of needles. Health professionals, nursery staff, and teachers should also be trained in anaphylaxis after graduation [13].

Safe alternative drugs were found for the cases presenting with DHRs. Diagnostic skin tests were performed only in local and general anesthetic drug allergies, due to the reasons physicians are more likely to use safe alternative drugs in inappropriate conditions to perform skin tests (lack of safe test areas, time limitation, inability to describe the culprit drug, or patients using drugs that affect the test technique, etc.)

In our center, cross-reactive NSAIDs are avoided. Anti-inflammatory treatments with

meloxicam/nimesulide (which preferentially inhibits the cyclo-oxygenase: COX-2 enzyme) were preferred as safe alternative drugs. In beta-lactam, allergic cases, oral provocation tests with macrolides were referred to as safe anti-microbial treatments, and DHRs were not observed in patients by the literature [14-17].

The most important limitation of our study is its retrospective design and the fact that the data is based on patients' statements. Confirmation/diagnostic tests or drug provocations have not been performed to reveal the culprit drug.

The main factors in the failure of drug diagnosis and provocation tests are the lack of allergy clinics with adequate safety, the long-term duration of the tests, and the lack of trained personnel (the preparation of the tests and the failure to provide appropriate treatment in case of an allergic reaction).

HSRs may develop during drug diagnosis and provocation tests. In these cases, the need for emergency assistance, advanced follow-up, environmental conditions to perform the first-line treatments, and trained personnel are required. Considering all these needs, if possible, performing a drug provocation test with an alternative drug is a more reliable and time-saving method.

All cases were managed with an alternative drug recommendation. For this reason, DHRs were classified as only immune/non-immune or immediate/delayed type.

However, in the literature, drug provocation tests showed low but different positivity rates between 4% and 27% [18-20]. Provocation tests are the gold standard in the diagnosis of true drug allergy and should be applied in the presence of safe conditions.

In conclusion, our study is remarkable in terms of the rarity of the actual DHR frequency among the cases admitted to the tertiary allergy immunology outpatient clinic in the Northeastern region of Turkey. When the demographic and clinical findings of these cases were examined, it was observed that the cases were frequently familiar with culprit drugs and approximately half of the cases had a history of anaphylaxis. However, the frequency of administration of adrenaline in cases of anaphylaxis was <50%. In addition, DHRs very rarely require hospitalization and can be treated on an outpatient basis. This result shows us that it is necessary to raise awareness before and after graduation about the diagnosis and treatment of anaphylaxis in emergency and primary health care services.

Conflict Of Interest

The authors have no conflict of interest to declare.

References

1. Wilkerson RG. Drug Hypersensitivity Reactions. Immunol Allergy Clin North Am. 2023 Aug;43(3):473-489.
2. Suh DC, Woodall BS, Shin SK, Hermes-De Santis ER. The clinical and economic impact of adverse drug reactions in hospitalized patients. Ann Pharmacother. 2000 Dec;34(12):1373-9.
3. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998 Apr 15;279(15):1200-5
4. Kalyoncu AF, Karakoca Y, Demir AU, Alpar R, Shehu V, Cöplü L, Sahin AA, Baris YI. Prevalence of asthma and allergic diseases in Turkish university students in Ankara. Allergol Immunopathol (Madr). 1996 Jul-Aug;24(4):152-7.
5. Bavbek S, Erkekol FÖ, Celik GE, Gönüllü I, Misirligil Z. Self-reported prevalence of hypersensitivity reactions against drugs among medical students: does awareness cause any difference? Pharmacoepidemiol Drug Saf. 2011 Feb;20(2):154-61.
6. Kurt E, Demir AU, Cadirci O. Immediate type drug hypersensitivity reactions and associated risk factors in an adult Turkish men population. Iran J Allergy Asthma Immunol. 2010 Dec;9(4):245-50.
7. Çelik GE, Karakaya G, Öztürk AB, Gelincik A, Abadoğlu O, Sin A, Damadoğlu E, Yılmaz İ, Demirtürk M, Dursun B, Özdemir SK, Çelikel S, Değirmenci P, Bozkurt B, Göksel Ö, Erkekol FÖ, Aydın Ö, Kavut AB, Kırmaz C, Kalpaklıoğlu F, Büyüköztürk S, Kalyoncu F. Drug allergy in tertiary care in Turkey: results of a national survey. The ADAPT study: adult drug allergy perception in Turkey. Allergol Immunopathol (Madr). 2014 Nov-Dec;42(6):573-9.
8. Mueller HL. Diagnosis and treatment of insect sensitivity. J Asthma Res. 1966 Jun;3(4):331-3.
9. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, Brockow K, Pichler WJ, Demoly P; European Network for Drug Allergy (ENDA); EAACI interest group on

drug hypersensitivity. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy. 2003 Sep;58(9):854-63.
10. Demoly P, Gomes ER. Drug hypersensitivities: definition, epidemiology, and risk factors. Eur Ann Allergy Clin Immunol. 2005 Jun;37(6):202-6.
11. Gomes E, Cardoso MF, Praça F, Gomes L, Mariño E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. Clin Exp Allergy. 2004 Oct;34(10):1597-601.
12. Dorner T, Lawrence K, Rieder A, Kunze M. Epidemiology of allergies in Austria. Results of the first Austrian allergy report. Wien Med Wochenschr. 2007;157(11-12):235-42.
13. Muraro A, Worm M, Alviani C, Cardona V, DunnGalvin A, Garvey LH, Riggioni C, de Silva D, Angier E, Arasi S, Bellou A, Beyer K, Bijlhout D, Bilò MB, Bindslev-Jensen C, Brockow K, Fernandez-Rivas M, Halken S, Jensen B, Khaleva E, Michaelis LJ, Oude Elberink HNG, Regent L, Sanchez A, Vlieg-Boerstra BJ, Roberts G; European Academy of Allergy and Clinical Immunology, Food Allergy, Anaphylaxis Guidelines Group. EAACI guidelines: Anaphylaxis (2021 update). Allergy. 2022 Feb;77(2):357-377.
14. Knowles SR, Drucker AM, Weber EA, Shear NH. Management options for patients with aspirin and nonsteroidal antiinflammatory drug sensitivity. Ann Pharmacother. 2007 Jul;41(7):1191-200.
15. Kowalski ML, Makowska J. Use of nonsteroidal anti-inflammatory drugs in patients with aspirin hypersensitivity: safety of cyclo-oxygenase-2 inhibitors. Treat Respir Med. 2006;5(6):399-406.
16. Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, Bousquet P, Celik G, Demoly P, Gomes ER, Niżankowska-Mogilnicka E, Romano A, Sanchez-Borges M, Sanz M, Torres MJ, De Weck A, Szczeklik A, Brockow K. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs)- classification, diagnosis and management: review of the EAACI/ENDA(#) and GA2LEN/HANNA*. Allergy. 2011 Jul;66(7):818-29.
17. Çelik GE, Erkekol FÖ, Aydın Ö, Demirel YS, Mısırlıgil Z. Are drug provocation tests still necessary to test the safety of COX-2 inhibitors in patients with cross-reactive NSAID hypersensitivity? Allergol Immunopathol (Madr). 2013 May-Jun;41(3):181-8.
18. Messaad D, Sahla H, Benahmed S, Godard P, Bousquet J, Demoly P. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. Ann Intern Med. 2004 Jun 15;140(12):1001-6.
19. Na HR, Lee JM, Jung JW, Lee SY. The usefulness of drug provocation tests in children with a history of adverse drug reaction. Korean J Pediatr. 2011 Jul;54(7):304-9.
20. Aun MV, Bisaccioni C, Garro LS, Rodrigues AT, Tanno LK, Ensina LF, Kalil J, Motta AA, Giavina-Bianchi P. Outcomes and safety of drug provocation tests. Allergy Asthma Proc. 2011 Jul-Aug;32(4):301-6.

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Childhood PFAPA Syndrome Cases in a University Hospital in Turkey: A 10-Year Analysis

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ABSTRACT

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is characterized by recurrent fever attacks every 3-6 weeks lasting 3-6 days, associated with at least one of the three main symptoms. This study aimed to evaluate the demographic, clinical features, laboratory findings, and effectiveness of the applied treatment in patients with PFAPA syndrome.
A total of 73 patients diagnosed with PFAPA syndrome, aged between 0-18 years, who presented to Sivas Cumhuriyet University Hospital Pediatric Outpatient Clinic between 01.01.2012 and 31.12.2022, were included in this study. Demographic data such as age, gender, symptoms, laboratory findings, treatment and efficacy of the treatment were analysed.
Out of the 73 patients, 34 (46.6%) were female and 39 (53.4%) were male. The mean and median age at diagnosis were 3.85±1.47 years and 3.30 (1.1-7.5) years, respectively. The most common presenting complaint was fever. Fever was present in 64 (87.6%) of the 73 patients. Pharyngitis was observed in 56 (76.7%) patients, cervical adenitis in 26 (35.6%), cryptic tonsillitis in 12 (16.5%), and aphthous stomatitis in 15 (20.6%). Leukopenia and neutropenia were not detected in patients at the time of diagnosis. Neutrophilia was observed in 59 (80.8%) patients, and leukocytosis in 64 (87.7%) patients. Prior to treatment, CRP levels were found to be higher than the reference value of 8 mg/L in all patients. Prior to treatment, ESR values were within normal range (lower than 20 mm/h) in 10 (13.7%) patients and higher than 20 mm/h in 63 (86.3%) patients. Tonsillectomy was performed in 10 (13.7%) of 73 patients.
The possibility of PFAPA syndrome should be considered in the differential diagnosis of patients younger than 5 years of age who present with recurrent episodes of fever and tonsillitis and whose fever does not decrease despite antibiotic treatment. In this way, early diagnosis can be made, unnecessary antibiotic use can be avoided and thus unnecessary investigations, treatment and hospitalisations can be prevented.

Keywords: Periodic fever, PFAPA, children

Türkiye'de Bir Üniversite Hastanesindeki Çocukluk Çağı PFAPA Sendromu Vakaları: 10 Yıllık Analiz

Süreç

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ÖZ

Ateş, aftöz stomatit, farenjit ve servikal adenit (PFAPA) sendromu , üç ana belirtiden en az biriyle ilişkili, her 3-6 haftada bir tekrarlayan, 3-6 gün süren ateş atakları ile karakterizedir. Bu çalışmada, PFAPA sendromu hastalığının demografik, klinik özellikleri,laboratuvar bulguları ve uygulanan tedavinin etkinliğinin değerlendirilmesi amaçlanmıştır.
Bu çalışmaya Sivas Cumhuriyet Üniversitesi Hastahanesi Pediatri Polikliniğine 01.01.2012-31.12.2022 tarihleri arasında başvuran 0-18 yaş grubu hastalardan PFAPA Sendromu tanısı alan 73 hasta dahil edildi. Çalışmaya dahil edilecek hastalarda yaş, cinsiyet gibi demografik verileri, semptomlar, laboratuvar bulguları, uygulanan tedavi ve tedavinin etkinliği incelendi.
Yetmiş üç hastanın 34'ü (%46,6) kız , 39'u (%53,4) erkekti. Ortalama ve medyan tanı yaşı ise sırasıyla 3,85±1,47 yıl ve 3,30 (1,1–7,5) yıldı. En yaygın başvuru şikayeti ateş idi. 73 hastadan 64'ünde (%87,6) ateş şikayeti mevcuttu. Hastaların 56'sında (%76,7) farenjit, 26'sında (%35,6) servikal lenfadenit, 12'sinde (%16,5) kriptik tonsilit, 15'inde (%20,6) aftöz stomatit mevcuttu. Tanı anında hastalarda lökopeni ve nötropeni saptanmadı. Nötrofil yüksekliği 59 (%80,8) hastada ve lökositoz 64 (%87,7) hastada görüldü. Tedavi öncesi tüm hastaların CRP değeri referans değeri olan 8 mg/L'den yüksek bulundu. Tedavi öncesi ESH değeri hastaların 10 (% 13,7)'unda normal değerlerde (20 mm/h'den düşük), 63 (% 86,3) hastada ise 20 mm/h'den yüksekti. 73 hastadan 10'una (%13,7) tonsillektomi uygulandı.
Tekrarlayan ateş ve tonsilit atakları ile getirilen, antibiyotik tedavisine rağmen ateşi düşmeyen 5 yaşından küçük hastalarda ayırıcı tanıda PFAPA sendromu olasılığı göz önünde bulundurulmalıdır. Bu sayede erken tanı konabilir, gereksiz antibiyotik kullanımından kaçınılabilir ve böylelikle gereksiz tetkik, tedavi ve hastaneye yatışların önüne geçilebilir.

Anahtar sözcükler: Periyodik ateş, PFAPA, çocuklar

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Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is characterized by recurrent fever attacks lasting 3-6 days, occurring every 3-6 weeks, and associated with at least one of the three main symptoms.[1,3] Fever attacks usually have minimal or no response to antipyretic medications. Patients are asymptomatic between attacks and have normal growth and development. Other symptoms that may occur during fever attacks include headache, joint pain, myalgia, nausea, vomiting, and abdominal pain [4,6]. PFAPA syndrome usually begins before school age and lasts until around 10-11 years old, although some cases are diagnosed in adults. Despite being the most common cause of recurrent fever in children, the true incidence of PFAPA syndrome is unknown due to the rarity of its diagnosis and frequent misdiagnosis, such as bacterial tonsillitis, leading to unnecessary administration of antibiotics [7,8]. The genetic origin of PFAPA syndrome is a matter of debate and several studies suggest that inflammation-related genes may play a role in this autoinflammatory syndrome. Although the exact pathogenesis is unknown, there is an increase in inflammatory cytokines in the blood and affected tissues and dysregulation of the receptors of these cytokines [9,10]. The diagnosis of PFAPA syndrome is based on clinical criteria and excluding other possible causes of recurrent fever in children [11]. During febrile episodes, neutrophils, acute phase reactants and white blood cells are elevated. All inflammatory parameters are normal between attacks [11,12]. In the treatment of PFAPA syndrome attacks, the administration of a single or two doses of steroids during an attack leads to a dramatic improvement in symptoms [13,14]. The aim of this study was to evaluate the demographic and clinical characteristics, laboratory findings and efficacy of the treatment of PFAPA syndrome.

Material Method

In this study, 73 patients aged 0-18 years who were admitted to Sivas Cumhuriyet University Hospital Paediatrics Outpatient Clinic between 01.01.2012-31.12.2022 and diagnosed with PFAPA Syndrome were included. Demographic data such as age, gender, symptoms, laboratory findings, treatment and efficacy of the treatment were analysed. In complete blood count, leukocyte, lymphocyte, neutrophil, platelet and haemoglobin values were evaluated according to normal values determined according to age. Normal platelet count is 150-450x109 litres. Platelet count below 150x109 /L was considered for thrombocytopenia. Platelet count above 450x109 /L was considered for thrombocytosis. For anaemia, the guidelines of the National Health and Nutrition Examination Survey (NHANES-III) were used as the basis. Leukopenia was defined as a total leukocyte count <4,000/µL. Neutropenia was defined as a total neutrophil count <1500/µL. For C-Reactive Protein (CRP) analyzed in the Biochemistry Laboratory of the Cumhuriyet University Faculty of Medicine Research and Application Hospital, the normal values are 0-8 mg/L. For Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT), the normal values are 0-40 U/L. For Erythrocyte Sedimentation Rate (ESR), the normal values are between 0-20 mm/hour.

Ethics of the Study

The study was approved by the Clinical Research Ethics Committee of Sivas Cumhuriyet University (2022-12/10) and conducted in accordance with the principles of the Helsinki Declaration.

Statistical Analysis

SPSS Windows Version 22 package program was used for statistical analysis. The data obtained from our study were loaded into the SPSS 22.0 programme and Wilcoxon test was used to compare two measurement values obtained at different times in the same individuals since the data did not conform to normal distribution, and Chi Square Test and Fisher Exact Test were used in 2x2 layouts and multi compartment layouts in the evaluation of the data obtained by counting. Our data were expressed as arithmetic mean, median, standard deviation, number of individuals and % (percentage) in the tables and the error level was taken as 0.05.

Results

Out of seventy-three patients, thirty-four (46.6%) were female and thirty-nine (53.4%) were male. The mean and median age of diagnosis were 3.85±1.47 years and 3.30 (1.1-7.5) years, respectively. The most common presenting complaint was fever. Among the seventy-three patients, sixty-four (87.6%) had a complaint of fever. When we referred to the period in which fever attacks occurred and the frequency of the attacks, we found information on forty-seven patients in their files, which was as follows: twenty-five (34.2%) patients (53.19% of the forty-seven patients) had attacks every thirty days, and twenty-two (30.1%) patients (46.80% of the forty-seven patients) had attacks between fifteen and thirty days. In the patients, fifty-six (76.7%) had

pharyngitis, twenty-six (35.6%) had cervical lymphadenitis, twelve (16.5%) had cryptic tonsillitis, and fifteen (20.6%) had aphthous stomatitis (Table 1).

Table 1. Demographic characteristics, clinical findings and symptoms of the patients

Gender	n (%)
Male	39 (53,4)
Girl	34 (46,6)
Age at diagnosis	**Year**
Mean±SD	3,85 ±1,47
Median (range)	3,30 (1,1-7,5)
Symptoms	**n (%)**
Fever	64 (87,6)
Abdominal pain	12 (16,4)
Sore throat	11 (15)
Vomiting	8 (11)
Sores in the mouth	6 (8,2)
Nausea	4 (5,5)
Cough	2 (2,7)
Results	**n (%)**
Fever	64 (87,6)
Pharyngitis	56 (76,7)
Cervical adenitis	26 (35,6)
Aphthous stomatitis	15 (20,6)
Cryptic tonsillitis	12 (16,5)

* SD: standard deviation

All patients received outpatient treatment. Seventeen (23.3%) patients had a history of frequent tonsillitis attacks in their first-degree relatives. During the attacks, 1 mg/kg of intravenous/intramuscular methylprednisolone was used for treatment, and all patients had a dramatic response. Laboratory tests were examined before (during the attack) and after treatment. Before treatment (during the attack), the mean white blood cell count was 14.55±4.26 /mm3, and the mean neutrophil count was 10.04±3.65 /mm3. After treatment, the mean white blood cell count was 8.45±2.10 /mm3, and the mean neutrophil count was 4.41±1.81 /mm3. Leukopenia and neutropenia were not detected in patients at the time of diagnosis. Neutrophilia was observed in fifty-nine patients (80.8%), and leukocytosis was observed in sixty-four patients (87.7%). The number of patients with normal leukocyte count was nine (12.3%), and the number of patients with normal neutrophil count was thirteen (17.8%). After treatment, no cases of leukopenia or neutropenia were observed. Thirty-three patients (45.2%) had normal white blood cell count, and six patients (8.2%) had leukocytosis. After treatment, the neutrophil count was normal in thirty-seven patients (50.7%) and high in two patients (2.7%).

Before treatment (during the attack), the average CRP value was 69.17±48.60 mg/dl, and the average ESR value was 36.44±16.16 ml/h. After treatment, CRP values were examined in 34 patients and ESR values in 24 patients. The average CRP value was 7.30±7.01 mg/dl, and the average ESR value was 11.33±4.10 ml/h. The biochemical values of the patients, including liver and kidney function tests, were normal before and after treatment (Table 2 and Table 3). Before treatment (during the attack), the CRP value of all patients (100%) was found to be higher than the reference value of 8 mg/L. After treatment, CRP value was found to be lower, i.e., normal, than the reference value of 8 mg/L in 24 (32.9%) patients, and higher in 10 (13.7%) patients. Before treatment, the ESR value was within the normal range (less than 20 mm/h) in 10 (13.7%) patients, and higher than 20 mm/h in 63 (86.3%) patients. After treatment, the ESR value was lower than the reference value of 20 mm/h in 24 (32.9%) patients, and there were no patients with high ESR values. Tonsillectomy was performed in 10 (13.7%) of 73 patients.

Table 2. Laboratory findings of the patients before treatment (during the attack)

Mean±SD	Median	Min.-max.	Total number of patients	
Leukocytes (/mm3)	14,55±4,26	13,61	6,07-26,89	73/73
Neutrophils (/mm3)	10,04±3,65	9,40	3,10-20,70	73/73
Haemoglobin (g/dl)	12,48±0,78	12,50	10,5-14,2	73/73
Platelets (/mm3)	318,47±83,80	312	179-596	73/73
ALT (U/L)	14,21±4,57	14	5-31	73/73
AST (U/L)	28,48±5,66	29	17-44	73/73
CRP (mg/dl)	69,17±48,60	73,05	14,51-247	72/73
ESR (mm/hour)	36,44±16,16	33	14-90	73/73

max: maximum, min: minimum, SD: standard deviation

Table 3. Laboratory findings of the patients after treatment

Mean±SD	Median	Min.-max.	Total number of patients	
Leukocytes (/mm3)	8,45±2,10	8,33	4,13-14,11	39/73
Neutrophils (/mm3)	4,41±1,81	4,38	1,64-8,95	39/73
Hemoglobin (g/dl)	12,81±0,87	12,7	11,2-15,8	39/73
Platelets (/mm3)	339,74±80,99	324	195-587	39/73
ALT (U/L)	17,04±5,25	16	17-40	52/73
AST (U/L)	26,30±6,19	25,50	10-30	50/73
CRP (mg/dl)	7,30±7,01	5,51	1,09-34,20	34/73
ESR (mm/hour)	11,33±4,10	11,50	5-19	24/73

max: maximum, min: minimum, SD: standard deviation

Discussion and Conclusion

Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis (PFAPA) syndrome is a disease characterized by recurrent fever attacks lasting 3-6 days, occurring every 3-6 weeks and associated with at least one of the three main symptoms [1,3]. In PFAPA syndrome, no gender-specific identification has been made, and in our study, the number of male patients with PFAPA syndrome was 39 (53.4%), which was higher. The majority of cases occur before the age of 5 [15]. In this study, the mean and median age of diagnosis for both girls and boys were 3.85 ± 1.47 years and 3.30 (1.1–7.5) years, respectively. PFAPA syndrome is the most common cause of recurrent fever in children [1]. In our study, the most common complaint was also fever. Fever was present in 64 out of 73 patients (87.6%). While the frequency of aphthous stomatitis in PFAPA syndrome cases is reported to range between 40% and 80% in the literature, aphthous stomatitis was present in 15 (20.6%) patients in our study [1,16]. This result may be related to the inability of young children to describe their condition and the less painful nature of the ulcers. In the literature, the attack interval is reported to recur every 3-6 weeks with an average interval of 30 days [1-3]. In our study, the duration of fever attacks was 30 days in 25 (34.2%) patients and between 15 and 30 days in 22 (30.1%) patients. Another notable finding in our study was that 17 patients (23.3%) had a history of frequent tonsil attacks in their first-degree relatives. It has been reported in studies that PFAPA cases are familial [17,18]. Leukocytosis and neutrophilia were present in our patients' laboratory findings.

Consistent with our study data, it has been reported that in PFAPA, inflammation occurs as a result of activation of the innate immune system, and neutrophil-leukocyte counts increase during febrile periods [1]. Inflammatory variables such as CRP and ESR increase during the attack period [19]. In our study, the CRP value of all patients before treatment (during the attack period) was found to be higher than the reference value of 8 mg/L. The ESR value before treatment (during the attack period) was higher than 20 mm/h in 63 patients (86.3%). Biochemical values, including liver and kidney function tests, were normal in patients during the attack period.

In the literature, it has been indicated that steroid treatment in PFAPA syndrome promptly stops flare-ups [20]. In our study, all of our patients (100%) had a dramatic response to methylprednisolone treatment. Tonsillectomy was performed in 10 of 73 patients (13.7%) in our study. Tonsillectomy and corticosteroids administered during attacks continue to be the most effective treatment [21]. The main limitations of our study are its retrospective design and the short duration of patient follow-up. The short follow-up period did not allow us to monitor the clinical response in patients who underwent tonsillectomy. In conclusion, the possibility of PFAPA syndrome should be considered in the differential diagnosis of patients younger than 5 years of age who present with recurrent fever attacks and whose fever does not decrease despite antibiotic treatment. When PFAPA syndrome is diagnosed, methylprednisolone treatment should be administered at the time of the attack. In this way, early diagnosis can be made, unnecessary antibiotic use can be avoided and unnecessary investigations, treatment and hospitalisations can be prevented.

Conflict of Interest and Financial Disclosure

The authors declare no conflicting interests. The authors also declare that they did not receive any financial support for this study.

References

1. Lazea C, Damian L, Vulturar R, Lazar C. PFAPA Syndrome: Clinical, Laboratory and Therapeutic Features in a Single-Centre Cohort. Int J Gen Med. 2022 Aug 29;15:6871-80.

2. Marshall GS, Edwards KM, Butler J, Lawton AR. Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. J Pediatr. 1987;110:43–46.

3. Otar Yener G, Aktaş İ, Altıntaş Meşe C, Çakan M. Does having MEFV gene sequence variants affect the clinical course and colchicine response in children with PFAPA syndrome? Eur J Pediatr. 2022 Nov 15:1-7.

4. Cochard M, Clet J, Le L, et al. PFAPA syndrome is not a sporadic disease. Rheumatology. 2010;49:1984–87.

5. Dammeyer KL, Schneider A, April MM, Kahn PJ. Synchronous disease onset and flares in siblings with PFAPA. Pediatr Rheumatol Online J. 2022 Oct 5;20(1):87.

6. Rydenman K, Fjeld H, Hätting J, Berg S, Fasth A. Epidemiology and clinical features of PFAPA: a retrospective cohort study of 336 patients in western Sweden. Wekell P.Pediatr Rheumatol Online J. 2022 Sep 15;20(1):82.

7. Kanık A, Eliaçık K, Kanık ET, Demirçelik Y, Demir BK. A comparative study for the clinical features in children with PFAPA syndrome who were diagnosed before and after the age of five. Int J Pediatr Otorhinolaryngol. 2022 Jul;158:111153.

8. Banday AZ, Joshi V, Arora K,et al. Challenges in the diagnosis of periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome in developing countries-A decade of experience from North India. Front Immunol. 2022 Sep 20;13:958473.

9. Espin Diaz PC, Singh K, Kher P, et al. Periodic Fever in Children: Etiology and Diagnostic Challenges. Cureus. 2022 Jul 25;14(7):e27239.

10. Kaynak D, Yildiz M, Sahin S, et al. NLRP3 gene variants and serum NLRP3 levels in periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. Clin Rheumatol. 2022 Sep 10. doi: 10.1007/s10067-022-06370-1. Online ahead of print.

11. Okamoto CT, Chaves HL, Schmitz MJ. Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome in children: a brief literature review. Rev Paul Pediatr. 2022 Jun 10;40:e2021087.

12. Førsvoll JA, Onymar K. C-reactive protein in the periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome. Acta Paediatr. 2007. PMID: 17937691.
13. Levinsky Y, Butbul Aviel Y, Ahmad SA, et al. PFAPA flares observed during COVID outbreak: can emotional stress trigger PFAPA attacks? A multicenter cohort study. Pediatr Rheumatol Online J. 2022 Jul 8;20(1):46.
14. Sopeña B, Araújo O, Freire M, Barrera-López L, José HR. Efficacy of Canakinumab in a Patient With Adult-Onset Glucocorticoid-Resistant Periodic Fever, Aphthous Stomatitis, Pharyngitis and Cervical Adenitis (PFAPA) Syndrome. Mod Rheumatol Case Rep. 2022 May 27:rxac043.
15. Wang A, Manthiram K, Dedeoglu F, Licameli GR. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome: A review. World J Otorhinolaryngol Head Neck Surg 2021 Jun 27;7(3):166-73.

16. Yıldız M, Haslak F, Adrovic A, Ülkersoy İ, Gücüyener N, et all. Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome: A Single-Center Experience. Turk Arch Pediatr 2022 Jan;57(1):46-52.doi: 10.5152/TurkArchPediatr.2021.21229.

17. Soriano A, Soriano M, Espinosa G, et al. Autoinflammatory Diseases and PFAPA Syndrome: Evidence-Based Approach and Proposal of a Practical Guide. Front Immunol 2020 Jun 3;11:865 doi: 10.3389/fimmu.2020.00865. eCollection 2020.

18. Wekell P, Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome PFAPA syndrome. Presse Med 2019 Feb;48(1 Pt 2):e77-e87.doi:10.1016/j.lpm.2018.08.016. Epub 2019 Jan 22.

19. Rydenman K, Berg S, Karlsson-Bengtsson A, Fasth A, Wekell P. PFAPA syndrome - An important differential diagnosis in children with recurrent fever. Lakartidningen 2019 Oct 29;116:FP9U.

20. Gaggiano C, Rigante D, Sota J, Grosso S, Cantarini L. Treatment options for periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome in children and adults: a narrative review. Clin Rheumatol 2019 Jan;38(1):11-17.doi: 10.1007/s10067-018-4361-2.

21. Batu ED, Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome: main features and an algorithm for clinical practice. Rheumatol Int 2019 Jun;39(6):957-970.doi: 10.1007/s00296-019-04257-0.

22. Burton MJ, Pollard AJ, Ramsden JD, Chong LY, Venekamp RP. Tonsillectomy for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA). Cochrane Database Syst Rev 2019 Dec 30;12(12):CD008669.doi:10.1002/14651858.CD008669.pub3.

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The Impact of Vitamin D and Acute Phase Proteins in the Diagnosis of Hyperemesis Gravidarum

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Research Article

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ABSTRACT

Hyperemesis gravidarum (HG) has severe, dramatic consequences, and the cause of this severe disease has not yet been determined clearly. It is known that hormonal, metabolic, immunological, and inflammatory agents may be effective in its etiology. Our study aimed to investigate the possible role of vitamin D, Lactate Dehydrogenase (LDH), Procalcitonin (PCT), and C-reactive Protein (CRP) in the etiology of HG. In this retrospective study, between June 1, 2021, and January 1, 2022, 110 pregnant women between 18 and 35 were admitted to the Obstetrics and Gynecology Polyclinic of the Sivas Cumhuriyet University Faculty of Medicine. Fifty-five patients diagnosed with HG were taken as a study group, and fifty-five healthy pregnant women not diagnosed with HG were taken as a control group. Obstetric data and serum vitamin D, LDH, PCT, and CRP values of pregnant women were detected retrospectively. When the groups with and without HG were compared, although the CRP and LDH levels were high in the HG group, they were not statistically significant (p=0.084, p=0.546). Vitamin D and PCT were significantly higher in the HG group than in the control group (p=0.001, p=0.047). Our study found high vitamin D and PCT levels in pregnant women with HG. Further studies with more participants are needed before these inflammatory markers can be used to diagnose HG.

Keywords: Hyperemesis gravidarum, CRP, vitamin D, inflammation, procalcitonin

D Vitamini ve Akut Faz Proteinlerinin Hiperemezis Gravidarum Tanısındaki Önemi

Süreç

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ÖZ

Hiperemezis gravidarum (HG), nedeni henüz belirlenememiş dramatik sonuçları olan bir durumdur. Etiyolojisinde hormonal, metabolik, immünolojik ve inflamatuar ajanların etkili olabileceği bilinmektedir. Bu çalışmada amaç HG etiyolojisinde vitamin D, LDH, Prokalsitonin ve CRP'nin olası rolünün araştırılmasıdır. Bu retrospektif çalışmada; 1 Haziran 2021-1 Ocak 2022 tarihleri arasında Sivas Cumhuriyet Üniversitesi Tıp Fakültesi Hastanesi Kadın Hastalıkları ve Doğum Polikliniği'ne başvuran 110 hasta çalışmaya dahil edilmiştir. 5-13. gebelik haftasında HG tanısı alan 18-35 yaşlarındaki 55 gebe çalışma grubu, HG tanısı konulmayan 55 sağlıklı gebe ise kontrol grubu olarak değerlendirilmeye alındı. Gebelerin obstetrik verileri ve serum vitamin D, LDH, Prokalsitonin ve CRP değerleri retrospektif olarak değerlendirildi. HG'li ve HG'siz gruplar karşılaştırıldığında, HG grubunda CRP ve LDH düzeyleri yüksek olmasına rağmen istatistiksel olarak anlamlı farklılık bulunmadı (p=0.084, p=0.546). HG grubunda; Vitamin D ve Prokalsitonin kontrol grubuna göre anlamlı derecede yüksekti (p=0.001, p=0.047). Çalışmamızda HG'li gebelerde D vitamini ve Prokalsitonin düzeylerinin yüksek olduğunu saptadık. Bu inflamatuar belirteçlerin HG tanısında kullanılabilmesi için daha fazla katılımcıyla daha ileri çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Hiperemezis gravidarum, CRP, D vitamini, inflamasyon, prokalsitonin

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Introduction

The main symptoms of pregnancy are nausea and vomiting. It is known that 70-80% of pregnant women experience nausea and vomiting that begin 2-4 weeks after fertilization, increase in severity and peak in the 9-16th week of gestation, and improve in the 20-22nd week of pregnancy. In a small number of pregnant women, complaints continue until birth [1,2]. Clinical manifestations such as treatment-resistant vomiting, electrolyte imbalance, dehydration, and ketonuria, accompanied by weight loss, are diagnosed as "Hyperemesis Gravidarum (HG)." HG is less common than pregnancy nausea and occurs in 0.2-3.6% of all pregnant women. It is the most common cause of hospitalization in the first trimester of pregnancy and causes serious labor and costs [3]. The exact pathophysiology of HG is still unclear. Its etiology is thought to be multifactorial and is associated with hormonal, metabolic, immunological, psychological, and genetic factors [4,5]. HG risk factors are previous pregnancies, multiple pregnancies, female fetuses, history of psychiatric illness, high and low body mass index before pregnancy, young age, black or Asian ethnicity, and type I diabetes [6-9]. Smoking has been found to reduce the risk of HG [10]. In patients with malnutrition whose symptoms persist into the second trimester, HG may lead to adverse pregnancy and perinatal outcomes [8,11]. Studies show that HG causes poor pregnancy outcomes such as premature birth, low birth weight, and intrauterine growth retardation [4,12,13]. Contrary to what would be expected in women with HG due to fasting, metabolic, and hormonal factors, the immune system is activated, and there is an increase in systemic inflammation [14,15]. Inflammation must be under control during pregnancy; otherwise, there will be problems with the implantation of the semi-allogeneic fetus into the endometrium and the healthy continuation of the pregnancy [16]. Physiological regulation of the excessive immune response in pregnancy will prevent the rejection of the semi-allogeneic fetus. A significant association between HG and markers of inflammation, such as C-reactive protein (CRP), vaspin, interleukin-6 (IL-6), and sirtuin, has been reported in literature [17].

Complications in HG increase as the severity of the disease increases. Early detection and prompt treatment will help relieve physical and psychological symptoms in women at risk for HG [18].

Based on this idea, we aimed to evaluate acute phase reactants such as Procalcitonin (PCT), CRP, Lactate Dehydrogenase (LDH), and 25(OH) Vitamin D levels in patients with HG to find new markers that may be effective in early diagnosis.

Materials and Methods

In our retrospective study, 110 patients between the ages of 18-35 who applied to the Obstetrics and Gynecology Polyclinic of Sivas Cumhuriyet University Faculty of Medicine Hospital between 1 June 2021 and 1 January 2022 at the 5th to 13th gestational week were included. As a study group, 55 patients with HG diagnosis were evaluated. As a control group, 55 healthy pregnant women who were not diagnosed with HG in the same age or gestational week range were assessed. The ethics committee approval of the study was obtained from the Faculty of Medicine of Sivas Cumhuriyet University (16.02.2022/ 2022-0248).

The diagnosis of HG was made according to the American College of Obstetricians and Gynecologists (ACOG) criteria. These criteria are having excessive nausea and vomiting with a weight loss of 5% compared to pre-pregnancy weight or having ketonuria with a weight loss of 3-5% and vomiting more than three times daily. Various questions such as age, gravity, parity, gestational week, at what gestational week the nausea-vomiting started, whether he used a drug for nausea-vomiting, whether he was related to his wife, the mother's body mass index (BMI), type of pregnancy (spontaneous/ovulation induction/IVF-IUI (In vitro fertilization- Intrauterine insemination)) were obtained from the files of these patients. Vitamin D (25(OH) vitamin D), PCT, LDH, and CRP results were found and noted from the patient's laboratory results.

In this study, gastroenteritis, gallbladder diseases, hepatitis, peptic ulcer, urinary tract stones, pyelonephritis, hyperthyroidism, hyperparathyroidism, migraine, vestibular disorders, pregestational and gestational diabetes, chronic liver and kidney failure, history of preeclampsia and chronic hypertension, multiple pregnancies, those with infection in the last three months, those with systemic infective diseases and smokers were excluded.

Statistical Analysis

The study used the SPSS 22.0 (Statistical Package for Social Sciences) program for statistical analysis. It was used in the statistical analysis of descriptive data (mean, standard deviation, frequency, rate, minimum, maximum). The suitability of quantitative data to the normal distribution was tested by Kolmogorov-Smirnov and Shapiro-Wilk tests. Study parameters were compared with the Independent Samples Test and Chi-Square test.

Results

55 pregnant with HG diagnosis and 55 healthy pregnant without HG diagnosis were included as a control group. The descriptive characteristics of pregnant women are shown in Table 1.

Table 1. The descriptive features of the pregnant women

	Hyperemesis gravidarum (*n*=55)	Control group (*n*=55)	*p*
Age†	27.4±4.4 (20-34)	27.4±4.0 (20-34)	> 0.05
Gravidity†	2.1±1.1 (1-6)	2.6±1.1 (1-6)	> 0.05
Parity†	1.0±1.0 (0-5)	1.2±0.9 (0-4)	> 0.05
Gestational week†	8.9±2.1 (5-12)	8.9±1.8 (6-12)	> 0.05
BMI†	24.0±4.0 (17.5-34.2)	25.1±2.9 (20.5-33.8)	> 0.05
Type of pregnancy*			
Spontaneous	47 (85.5)	46 (83.6)	> 0.05
Ovulation induction	4 (7.3)	6 (10.9)	> 0.05
IVF-IUI	4 (7,3)	3 (5.5)	> 0.05

† Continuous variables expressed as Mean ± Standard deviation (minimum-maximum).
* Categorical variables were expressed as frequency (percentage) values.
BMI, Body mass index; IVF-IUI, In vitro fertilization- Intrauterine insemination

The mean gestational week of nausea of the participants was 5.6±1.3 (4-10) in the HG group and 5.4±1.1 (4-9) in the control group, and there was no statistically significant difference between them (p=0.36). Neither the HG group nor the control group had any consanguineous marriages. The percentage of participants using anti-nausea medication in the HG group was 41.8 (23), and 52.7 percent (29) in the control group.

There was no significant difference between the two groups in terms of the rate of use of anti-nausea drugs (p= 0.25).

There were significant differences between the mean amounts of PCT and vitamin D between the two groups (p<0.05). The data for this analysis and the mean of CRP, PCT, vitamin D (25(OH) vitamin D), and LDH are shown in Table 2.

Table 2. Comparison of study data averages between groups

	Hyperemesis gravidarum (Mean ± SD)	Control group (Mean ± SD)	*t*	*p*
CRP	6.6±4.5	5.3±3.1	-1.748	0.084
Procalcitonin	0.6±0.07	0.4±0.009	-2.027	**0.047**
LDH	208±62.5	201±45.2	-0.606	0.546
Vitamin D	9.4±3.6	16±8.4	5.786	**0.001**

SD, standard deviation; *p*<0,05 statistical significance

Discussion

Although the cause of HG is still not established, it is known to be a severe problem characterized by hypovolemia, dehydration, and electrolyte disturbance. It is known that there is usually some systemic inflammation at every stage of pregnancy. Still, this situation does not cause complications in pregnancy because the immune response can regulate it. However, this inflammation occurs excessively in complicated pregnancies, and lousy pregnancy results because it cannot be controlled. Although its role in HG is unknown, it is known that systemic inflammation has increased [17].

Serum CRP is an acute phase reactant and one of the essential markers in the follow-up of the inflammatory process. Studies have reported increased CRP levels in women with HG that may contribute to the pathophysiology of HG compared with the control group [19-21]. A few studies have also found that CRP is similar in patients with HG compared to the control group. However, in these studies, oxidative stress, other markers of inflammation, and immunological factors have been shown to increase in patients with HG. These factors have been pointed out in the pathogenesis of HG [22]. Yılmaz et al. did not find a significant difference in CRP level between the groups in their study with 30 HG diagnosed and 30 control group participants [15]. In our study, although the CRP value was higher in the HG group than in the control group, there was no statistically significant difference. We think this difference may be due to the small number of participants and the ability of CRP to be affected by many other factors, such as nutrition and environmental factors.

Another elevated marker in systemic inflammatory growth is PCT. It's a calcitonin prohormone secreted in response to proinflammatory stimuli [23]. PCT is elevated explicitly in bacterial infections [24]. However, Yun Hu et al. compared the PCT values of healthy pregnant women and non-pregnant women in whose study the infection was excluded. They found an increase in healthy pregnant compared to non-pregnant women [25]. We have yet to encounter any scientific studies investigating PCT levels in HG in the literature. However, studies show that PCT increases in pregnancies complicated by conditions such as preeclampsia, diabetes mellitus (DM), and intrauterine growth retardation, where infection is excluded. It has been stated that the complications that occur in all these studies activate the immune system, which is in a particular order during pregnancy, and that PCT increases due to an excessive increase in immune response [26-29]. In this study, we investigated whether the increase in immune response due to overeating in pregnancy in HG, the cause of which has not yet been determined, causes changes in PCT levels. In the study, we found statistically significantly higher PCT in the HG group compared to the control group. We think high PCT is influential and essential in excessive nausea and vomiting in pregnancy.

During pregnancy, changes occur in the humoral and cell-mediated immune systems to protect the fetus and decidua from disruption by the mother's immune system [30]. Minagawa et al. agreed that HG results from an overactive immune system as a result of their study [31]. Several studies have shown an increased inflammatory response in patients with HG [32,33]. Vitamin D is known to have immunomodulatory and anti-inflammatory effects [34]. A study found that the 1α-Hydroxylase enzyme, which converts vitamin D into its active form in decidua in pregnancy, is the most commonly secreted in 1. trimester [35]. In vitamin D deficiency, the anti-inflammatory response, which should be at a certain level in pregnancy, is disrupted, and the inflammatory response increases. Since adequate immunotolerance is not achieved, decidualization is disrupted, and pregnancy complications such as abortion, preeclampsia, and hyperemesis occur [36]. In their study, Yılmaz et al. found no statistically significant difference between HG and the control group regarding vitamin D levels. Still, they found that vitamin D levels were lower in the HG group [15]. In the literature, vitamin D levels were significantly lower in HG patients compared to the control group [37,38]. In our study, confirming the literature, significantly lower vitamin D levels were found in the HG group than in the control group.

In studies by Calleja-Agius et al. and Kalagiri et al., they reported an increased systemic inflammatory response in pregnancy and increased complications, especially early pregnancy losses, in pregnancies complicated by HG [39,40]. Therefore, follow-up of systemic inflammatory markers is essential in the diagnosis, follow-up, and prevention of possible poor outcomes of HG.

Conclusion

In our study, although CRP and LDH levels were higher in the HG group than in the control group, no statistically significant difference was found. PCT and vitamin D levels were significantly higher in the HG group than in the control group. Many metabolic, environmental, and personal factors can influence inflammatory markers. It is also unclear whether this inflammatory increase in HG is elevated as a result or cause of HG.

Considering that our study was conducted with a limited number of samples applying to a single institution and was studied with few markers, although it is a guide for subsequent analyses, more features should be evaluated with a larger sample.

References

1. Nawaz M; Rishma; Afridi SG, Khan A, Shams S. Frequency of Hyperemesis Gravidarum and associated risk factors among pregnant women. J Pak Med Assoc. 2020 Apr;70(4):613-617.
2. Onder AB, Guven S, Demir S, Mentese A, Guvendag Guven ES. Biotin deficiency in hyperemesis gravidarum. J Obstet Gynaecol. 2019 Nov;39(8):1160-1163.
3. Koot MH, Grooten IJ, Post JAM Van Der, Bais JMJ, Ris-stalpers C, Lee MMG, et al. European Journal of Obstetrics & Gynecology and Reproductive Biology Determinants of disease course and severity in hyperemesis gravidarum. 2020;245:162–7.
4. Ioannidou P, Papanikolaou D, Mikos T, Mastorakos G, Goulis DG. European Journal of Obstetrics & Gynecology and Reproductive Biology Predictive factors of Hyperemesis Gravidarum : A systematic review. Eur J Obstet Gynecol. 2019; 238:178–87.
5. Yoneyama Y, Suzuki S, Sawa R, Araki T. Plasma adenosine concentrations increase in women with hyperemesis gravidarum. Clin Chim Acta. 2004;342(1–2):99–103.
6. Zhang Y, Cantor RM, MacGibbon K, Romero R, Goodwin TM, Mullin PM, et al. Familial aggregation of hyperemesis gravidarum. Am J Obstet Gynecol. 2011;204(3):230.e1-230.e7.
7. Fell DB, Dodds L, Joseph KS, Allen VM, Butler B. Risk factors for hyperemesis gravidarum requiring hospital admission during pregnancy. Obstet Gynecol. 2006;107(2):277–84.
8. Roseboom TJ, Ravelli ACJ, Van Der Post JA, Painter RC. Maternal characteristics largely explain poor pregnancy outcomes after hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol. 2011;156(1):56–9.
9. Fiaschi L, Nelson-Piercy C, Tata LJ. Hospital admission for hyperemesis gravidarum: A nationwide study of occurrence, reoccurrence and risk factors among 8.2 million pregnancies. Hum Reprod. 2016;31(8):1675–84.
10. Jenabi E, Fereidooni B. The association between maternal smoking and hyperemesis gravidarum: a meta-analysis. J Matern Neonatal Med. 2017;30(6):693–7.
11. Bolin M, Åkerud H, Cnattingius S, Stephansson O, Wikström AK. Hyperemesis gravidarum and risks of placental dysfunction disorders: A population-based cohort study. BJOG An Int J Obstet Gynaecol. 2013;120(5):541–7.
12. Coetzee RL, Cormack B, Sadler L, Bloomfield FH. Pregnancy and neonatal outcomes following hyperemesis gravidarum. J Dev Orig Health Dis. 2011;2(2):81–8.
13. Agmon N, Sade S, Pariente G, Rotem R, Weintraub AY. Hyperemesis gravidarum and adverse pregnancy outcomes. Arch Gynecol Obstet. 2019;300(2):347–53.
14. Oğlak SC, Aydin MF. Are neutrophil to lymphocyte ratio and platelet to lymphocyte ratio clinically useful for the prediction of early pregnancy loss? Ginekol Pol. 2020;91(9):524–7.
15. Yılmaz S, Cırık DA, Demirtaş C, Timur H, Şahin A, Danışman N, et al. Do vitamin D and high-sensitivity-C reactive protein levels differ in patients with hyperemesis gravidarum? A preliminary study. Turkish J Obstet Gynecol. 2016;13(3):123–6.
16. Christiansen OB, Nielsen HS, Kolte AM. Inflammation and miscarriage. Semin Fetal Neonatal Med.
2006;11(5):302–8.
17. Oğlak SC, Obut M. The Role of Systemic Inflammatory Markers in the Diagnosis of Hyperemesis Gravidarum. Muğla Sıtkı Koçman Üniversitesi Tıp Derg. 2020 Dec 29;7(3):124–7.
18. Kim HY, Cho GJ, Kim SY, Lee KM, Ahn KH, Han SW, Hong SC, Ryu HM, Oh MJ, Kim HJ, Kim SC. Pre-Pregnancy Risk Factors for Severe Hyperemesis Gravidarum: Korean Population Based Cohort Study. Life (Basel). 2020 Dec 26;11(1):12.
19. Aksoy H, Aksoy AN, Ozkan A, Polat H. Serum lipid profile, oxidative status, and paraoxonase 1 activity in hyperemesis gravidarum. J Clin Lab Anal. 2009;23(2):105–9.
20. Leylek OA, Toyaksi M, Erselcan T, Dokmetas S. Immunologic and biochemical factors in hyperemesis gravidarum with or without hyperthyroxinemia. Gynecol Obstet Invest. 1999;47(4):229–34.
21. Engin-Ustun Y, Tonguç E, Var T, Deveer R, Yilmaz N, Danisman N, et al. Vaspin and C-reactive protein levels in hyperemesis gravidarum. Eur Rev Med Pharmacol Sci. 2013;17(1):138–40.
22. Tunc SY, Agacayak E, Budak S, Tunc N, Icen MS, Findik FM, et al. Serum levels of neopterin , inflammatory markers and oxidative stress indicators in hyperemesis gravidarum. 2016;42(6):618–24.
23. Dockree S, Brook J, James T, Shine B, Vatish M. A pregnancy-specific reference interval for procalcitonin. Clin Chim Acta. 2021;513(October 2020):13–6.
24. Jekarl DW, Lee SY, Lee J, Park YJ, Kim Y, Park JH, et al. Procalcitonin as a diagnostic marker, and IL-6 as a prognostic marker for sepsis. Diagn Microbiol Infect Dis. 2013;75(4):342–7.
25. Hu Y, Yang M, Zhou Y, Ding Y, Xiang Z, Yu L. Establishment of reference intervals for procalcitonin in healthy pregnant women of the Chinese population. Clin Biochem. 2017;50(3):150–4.
26. Ma Y, Ye W, Tang Y. Gestational diabetes mellitus increases the baseline level of procalcitonin in maternal blood but not in umbilical cord blood in late pregnancy. A retrospective case-controlled study. Med (United States). 2019;98(11):1–5.
27. Karlı P, Özdemir AZ, Ayan D. Maternal serum and fetal cord blood C-reactive protein levels but not procalcitonin levels are increased in idiopathic intrauterine growth restriction. Med Sci Monit. 2019;25:6512–7.

28. Mangogna A, Agostinis C, Ricci G, Romano F, Bulla R. Overview of procalcitonin in pregnancy and pre-eclampsia. Clin Exp Immunol. 2019;198(1):37–46.
29. Lumbreras-Marquez MI, Lumbreras-Marquez J, Barraza-Salas M, Castillo-Reyther RA, De la Maza-Labastida S, Hernandez-Rayon YI, et al. Maternal and umbilical cord procalcitonin, high-sensitivity C-reactive protein, and interleukin-6 levels in preeclamptic and normotensive patients: A cross-sectional study. Pregnancy Hypertens. 2020;21(January):218–23.
30. Verberg MF, Gillott DJ, Al-Fardan N, Grudzinskas JG. Hyperemesis gravidarum, a literature review. Hum Reprod Update. 2005 Sep-Oct;11(5):527-39.
31. Minagawa M, Narita J, Tada T, Maruyama S, Shimizu T, Bannai M, et al. Mechanisms underlying immunologic states during pregnancy: Possible association of the sympathetic nervous system. Cell Immunol. 1999;196(1):1–13.
32. Kaplan PB, Gücer F, Sayin NC, Yüksel M, Yüce MA, Yardim T. Maternal serum cytokine levels in women with hyperemesis gravidarum in the first trimester of pregnancy. Fertil Steril. 2003;79(3):498–502.
33. Kuscu NK, Yildirim Y, Koyuncu F, Var A, Uyanik BS. Interleukin-6 levels in hyperemesis gravidarum. Arch Gynecol Obstet. 2003;269(1):13–5.
34. Yavuz D, Mete T, Yavuz R, Altunoğlu A. D Vitamini, Kalsiyum & Mineral Metabolizması, D Vitaminin İskelet Dışı Etkileri ve Kronik Böbrek Yetmezliğinde Nütrisyonel D Vitamini Kullanımı. Ankara Med J. 2014;14(4):162–71.
35. Zehnder D, Evans KN, Kilby MD, Bulmer JN, Innes BA, Stewart PM, et al. The ontogeny of 25-hydroxyvitamin D3 1α-hydroxylase expression in human placenta and decidua. Am J Pathol. 2002;161(1):105–14.
36. Sekizawa A, Sugito Y, Iwasaki M, Watanabe A, Jimbo M, Hoshi S, et al. Cell-free fetal DNA is increased in plasma of women with hyperemesis gravidarum. Clin Chem. 2001;47(12):2164–5.
37. Çelik S, Soyer C, Güvey H, Yaşar B, Yazıcıoğlu B, Türe E, et al. Hiperemezis gravidarumda önemli bir nokta: d vitamini ve tiroid fonksiyonları. Jinekoloji-Obstetrik ve Neonatoloji Tıp Derg. 2020 Jun 25;17(2):331–4.
38. Gürbüz T, Dokuzeylük Güngör N. Hiperemezis gravidarum etiyopatogenezinde vitamin D eksikliğinin rolü var mı ? Adıyaman Üniversitesi Sağlık Bilim Derg. 2018;4(2):761–71.
39. Calleja-Agius J, Jauniaux E, Pizzey AR, Muttukrishna S. Investigation of systemic inflammatory response in first-trimester pregnancy failure. Hum Reprod. 2012;27(2):349–57.
40. Kalagiri RR, Carder T, Choudhury S, Vora N, Ballard AR, Govande V, et al. Inflammation in Complicated Pregnancy and Its Outcome. Am J Perinatol. 2016;33(14):1337–56.

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Determination Of Changes in Vitamin D, Folic Acid, and Vitamin B12 Levels in Patients Presenting To The Emergency Department After Suicidal Interventions

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ABSTRACT

Depression is a psychological and physiological destruction process. In recent years, it has been one of the leading causes of public health problems in our country and in the world. Our aim in this study; To contribute to the literature in the light of the data we obtained by measuring the levels of vitamin D, folic acid and vitamin B12 in patients who applied to the emergency department after suicidal attempts.

In the study, vitamin D, folic acid and vitamin B12 levels in blood tests taken from patients who applied to Sivas Cumhuriyet University Faculty of Medicine Department of Emergency Medicine between July 2019 and December 2020 with suicide attempts and healthy volunteers selected in line with the criteria were retrospectively analyzed. Consent forms received from Sivas Cumhuriyet University ethics committee with decision number 2020-06/14 were read and signed by healthy volunteers similar in gender and age and the patient group included in the study. Groups were formed by taking detailed anamnesis and physical examinations from volunteers who agreed to participate in the research.

In our study, we compared the levels of vitamin D, folic acid and vitamin B12 in patients who applied to the emergency department after a suicide attempt with the normal population. Vitamin D and vitamin B12 levels were found to be significantly lower in the patient group compared to the control group.

Our current clinical study supports many studies in the literature, with the detection of low levels of vitamin D and vitamin B12 after the examinations of the patient group who came to the emergency room with a depressive episode and the control group.

Keywords: Depression, Suicidal Behavior, Vitamin D, Vitamin B12, Folic Acid

İntihar Girişimi Sonrası Acil Servise Başvuran Hastalarda D Vitamini, Folik Asit Ve Vitamin B12 Düzeylerindeki Değişikliklerin Belirlenmesi

Süreç

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ÖZ

Depresyon psikolojik ve fizyolojik bir yıkım sürecidir. Son yıllarda ülkemizde ve dünyada halk sağlığı sorunlarının önde gelen nedenlerinden biri olmuştur. Bu çalışmadaki amacımız; intihar girişimi sonrası acil servise başvuran hastalarda D vitamini, folik asit ve B12 vitamini düzeylerini ölçerek elde ettiğimiz veriler ışığında literatüre katkı sağlamaktır.

Araştırmada Temmuz 2019-Aralık 2020 tarihleri arasında Sivas Cumhuriyet Üniversitesi Tıp Fakültesi Acil Tıp Anabilim Dalı'na intihar girişimi ile başvuran hastalardan ve belirlenen sağlıklı gönüllülerden alınan kan testlerinde D vitamini, folik asit ve B12 düzeyleri belirlendi. Kriterler geriye dönük olarak analiz edildi. Sivas Cumhuriyet Üniversitesi etik kurulundan 2020-06/14 karar numaralı alınan onam formları, çalışmaya dahil edilen hasta grubu ve cinsiyet, yaş benzer sağlıklı gönüllüler tarafından okunup imzalandı. Araştırmaya katılmayı kabul eden gönüllülerden detaylı anamnez ve fizik muayeneleri alınarak gruplar oluşturuldu.

Çalışmamızda intihar girişimi sonrası acil servise başvuran hastalarda D vitamini, folik asit ve B12 vitamini düzeylerini normal popülasyonla karşılaştırdık. Hasta grubunda D vitamini ve B12 vitamini düzeyleri kontrol grubuna göre anlamlı olarak düşük bulundu.

Mevcut klinik çalışmamız, acil servise depresif atakla gelen hasta grubu ve kontrol grubunun muayeneleri sonrasında D vitamini ve B12 vitamini düzeylerinin düşük olduğunun tespiti ile literatürdeki birçok çalışmayı desteklemektedir.

Anahtar Kelimeler: Depresyon, İntihar Davranışı, D Vitamini, B12 Vitamini, Folik Asit

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Introduction

Suicidal behavior is the desire and act of ending one's own life. In many literature reviews, this behavior has been associated with depression, and important steps have been taken in terms of treatment within the scope of existing studies. Depression is the most common debilitating psychiatric illness, the physiopathology of which is related to many aspects of neurohumoral functions [1]. Depression is a process that increases psychological and physiological destruction if left untreated. More than 300 million people worldwide have major depressive disorder, which is increasing day by day[2]. According to the Centers For Disease Control and Prevention (CDC) data, there has been a continuous increase in suicidal behaviors in the last 10 years. Worldwide, more than 800,000 people die by suicide each year [3]. There is a diagnosable psychiatric disorder in most suicides, especially mood disorder [4]. The most frequent application and first intervention place of the patient population after suicidal behavior is emergency services. For this reason, clinical studies, especially in emergency services, for the current patient population have gained more importance in recent years.

Since vitamins and minerals contribute to many physiological processes in the biological cycle of the human body, a decrease in the function of many metabolic functions in the body can be observed in case of their deficiency. As a result, it can lead to chronic health problems in the long run. In order to ensure optimal health in the medium and long term, providing minimum vitamin supplementation to prevent deficiency symptoms should be an important public health issue [5]. Nutritional habits are accepted as one of the important reasons that provide the pathophysiological mechanisms in the formation process of psychiatric disorders [6].

Vitamin D plays an active role in calcium and bone metabolism, the endocrine system, and the hormonal cycle, but research over the past two decades has also revealed numerous biological effects, including immunomodulation, induction of cell differentiation, and inhibition of growth [7].

There is a very close relationship between vitamin B12 and folic acid metabolism. They are the main determinants of one-carbon metabolism in which S-adenosylmethionine (SAM) is formed. The SAM metabolite is the precursor of methyl groups, which are very important for the continuation of neurological functions in the body [8]. Vitamin B12 and folic acid supplementation may play a role in the prevention of megaloblastic anemias, some neuropsychiatric syndromes such as Alzheimer's-dementia and mood disorders. (9)

Our aim in this study is to contribute to the literature in the light of the data we obtained by measuring the levels of vitamin D, folic acid, and vitamin B12 in patients who applied to the emergency department after suicidal attempts.

Materials and Methods

In this study, α= 0.05; When β= 0.10 and (1- β)= 0.90, it was decided to include 35 individuals in each group, and the power of the test was found to be p=0.907.

In the study, the patient group of 35 people who applied to Cumhuriyet University Faculty of Medicine, Department of Emergency Medicine, between July 2019 and December 2020 after a suicide attempt was evaluated after detailed anamnesis and physical examination. While forming the control group in our study, a similar population was preferred in order to increase the reliability of the research in terms of age and gender. The control group was selected from a population similar to the patient group in terms of age and gender. The study was completely voluntary within the scope of the informed consent form for both groups.

~5 mL blood samples were taken into biochemistry tubes (red caps) from the forearm veins of healthy and patient volunteers who agreed to participate in the study. The blood samples taken were kept at room temperature for 5 minutes. After waiting, it was placed in a centrifuge at 4000 rpm for 5 minutes. was centrifuged. The resulting supernatant, ~400 µL, was transferred to at least two Ephendorf tubes and stored at -200C until the study was performed. When the desired number of patients was reached, the samples were removed, brought to room temperature and measured according to the kit procedure specified by the manufacturer.

B12, Folic Acid, Vitamin D levels were measured from plasma/serum samples obtained from patients and healthy control groups. Data were analyzed using SPSS Data:23.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean ± standard deviation (SD). In the evaluation of the data, the significance test of the difference between the two means (Independent t test) was used when the parametric test assumptions were fulfilled, and the Man Whitney U test was used when the parametric test assumptions were not fulfilled.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Results

In our study, we analyzed the sociodemographic data of the patients, as well as the amount of vitamin D, folic acid, and vitamin B12 in plasma. We evaluated the comparative results of these vitamins, which manage many biological processes in human metabolism, in patient and control groups.

The mean age of 35 patients we evaluated was 30.13±11.69 years, and the mean age of 35 individuals in the control group was 30.95±9.48 years (p=0.17; p>0.05). (Table 1)

20 (57.1%) of the individuals in the patient group were female and 15 (42.9%) were male; 20 (57.1%) of the individuals in the control group were female and 15 (42.9%) were male (p=1; p> 0.05). (Table 1)

Table 1. Age and Gender Distribution Between Patient and Control Groups

	Patient Group N(%)	Control Group N(%)	Independent T Test
Gender			
Female	20 (57,1)	20 (57,1)	
Male	15 (42,9)	15 (42,9)	P=1
The Average Age	30,13±11,69	30,95±9,48	P=0,17

***** p<0,05**

When we compared the measured levels of vitamin D, folic acid, and vitamin B12 in patients admitted to the emergency department after a suicide attempt with the control group, we found a statistically significant difference between the two groups in terms of vitamin D and vitamin B12. (p<0.05)

Table 2. Comparison of Vitamin Values Between Patient and Control Groups

Vitamin Name	Patient Group Mean (Mean ± Sd)	Control Group Mean (Mean ± Sd)	P Values Student's t test
D Vitamin (mcg)	13,61	25,19	0,03*
Folic Acid (ng/mL)	7,76	8,30	0,49
B12 Vitamin (pg/ml)	274,77	359,05	0,001*

***P<0,05**

Discussion

In recent years, the frequency of suicidal behavior has gradually increased and has become a social problem and can lead to fatal consequences. Since the first place of application of the patient population is the emergency services, clinical evaluations and statistical analyses, especially in the emergency, should have clinical importance in the literature.

When we examine the data obtained in the study, When we grouped the patients admitted to the emergency department by gender after a suicide attempt, suicidal behavior was found to be higher in females (female: male ratio 1.53:1.15). Women have higher suicidal ideation and behavior patterns compared to men [10,11]. Our study's result is consistent with other studies (Table 1).

A study on risk factors in patients over 65 years of age who exhibit suicidal behavior, especially male gender, psychiatric history, stressors, and living alone, were found to be more significant in predicting completed suicides[12].

A low level of vitamin B12 was found in depressed patients, and in the results of studies conducted with the general population, a significant correlation was found between low vitamin B12 levels and depression[13]. Our study's results are similar to this.

Vitamin B12 is the precursor of methionine amino acid and SAM metabolite, which is responsible for the metabolism of neuropsychological functions in metabolism. Vitamin B deficiency and its treatment are extremely important, as disruption in the methylation cycle will increase the functionality of memory, dementia, and cognitive impairment. In this sense, it is very valuable to have low levels of vitamin B12 in patients who exhibit suicidal behavior. There are studies that show that vitamin B deficiency contributes to the complexity of depressive symptoms[14].

Studies also show that vitamin B12 supplementation reduces symptoms of depression and anxiety[15]. Considering the literature review, more comprehensive studies can be conducted on the possibility that patients with depressive moods take vitamin B12 supplements to reduce depressive episodes. In our study, vitamin B12 values measured in the patient population were significantly lower compared to the control group.

There are clinical studies showing that folic acid deficiency shows the same neuropsychological symptoms as vitamin B12 deficiency and increases the tendency to depression[16]. However, in our study, folic acid deficiency was not found to be significant between the patient and control groups. At the same time, folic acid level was found to be normal in the patient group in our study.

Recent studies have shown that insufficient vitamin D status is frequently observed in patients with depression[17]. In this sense, our current clinical study is similar to other studies. The results we found were lower in the patient group than in the control group and were compatible with other studies (Table 2). There are clinical data that analyze the relationship between vitamin D deficiency and depression and show improvements in depressive mood after vitamin D supplementation[18]. Although vitamin D deficiency is quite common in the world, it has been associated with anxiety disorders and major depressive disorders in many studies. There is also a clinical study in the literature that vitamin D supplementation reduces the symptoms of anxiety and depression[19]. However, a study that noted that there was no improvement in the present findings in the period observed after vitamin D supplementation in elderly patients with depressive symptoms and decreased physical functionality was also included in the literature[20].

In a study of clinical and preclinical studies examining the role of vitamin D on patients with dementia, mood disorders, and psychosis, it was thought that there was not enough evidence to say that vitamin D has a direct effect on the neuropsychological process[21].

CONCLUSIONS

Depression, which is an important health problem in recent years, may result in suicidal behavior and death. Studies conducted on this depressive patient population in emergencies, which are places of referral after suicide, are valuable.

Our study measured vitamin D, folic acid, and vitamin B12 levels in patients who applied to the emergency department after suicidal attempts. When we compared the levels of vitamin D, folic acid, and vitamin B12 in the patients who applied to the emergency department after a suicide attempt, we found that the levels of vitamin D and vitamin B12 were significantly lower in the patient group compared to the control group. The data we obtained in the literature review supported similar studies on depressive patients.

There is a need for more comprehensive studies by reach a larger number of patients and, in this context, vitamin-supported primary treatment planning on patient groups. Comprehensive studies

can be directed by using depression scales in order to have an objective evaluation of the same patient population after the treatments.

Our study has some limitations. The first and most important limitation is that it was studied with a relatively small group of patients. At the same time, our current study is single-centered and more comprehensive studies are needed. One of the limitations of our study was the inability to observe the clinical course after vitamin D levels returned to normal, as we correlated vitamin D and vitamin B12 deficiency, which we found in the patient group compared to the control group, with depressive mood.

It was thought that giving vitamin supplements to patients who presented with a suicide attempt and whose serum vitamin levels were low would prevent repeated suicide attempts. It is planned to conduct the study for a longer period of time (about 5 years) and with a larger number of patients to show whether patients with vitamin deficiencies who have attempted suicide in the future experience relapse after vitamin supplementation and whether the suicide attempt repeats.

References

1. Chunmei Geng, Abdul Sami Shaikh, Wenxiu Han, Dan Chen[1], Yujin Guo, Pei Jiang. Vitamin D and depression: mechanisms, determination and application, Asia Pac J Clin Nutr. 2019;28(4):689-694.
2. Gülseren Nur Ekinci, Nevin Sanlier. The relationship between nutrition and depression in the life process: A mini-review, Exp Gerontol. 2023; 172.
3. GBD 2015 Mortality and Causes of Death Collaborators, Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1459
4. Leo Sher, Maria A Oquendo. Suicide: An Overview for Clinicians, Med Clin North Am. 2023, 107(1):119-130.
5. Jean-Claude Guilland. What is a vitamin? Rev Prat. 2013, 63(8):1060-9.
6. Mohamed Said Boulkrane, Julia Fedotova, Valentina Kolodyaznaya, Vincenzo Micale, Filippo Drago, Annemieke Johanna Maria van den Tol, Denis Baranenko. Vitamin D and Depression in Women: A Mini-review Curr Neuropharmacol. 2020;18(4):288-300.
7. Adriana S Dusso, Alex J Brown, Eduardo Slatopolsky. Vitamin D, Am J Physiol Renal Physiol. 2005, 289(1):8-28.
8. Richard D Semba. Treatment of depression: time to consider folic acid and vitamin B12 J Psychopharmacol. 2005, 19(1):59-65.
9. Edward Reynolds. Vitamin B12, folic acid, and the nervous system, Lancet Neurol. 2006, 5(11):949-60.
10. Murphy, G.E. 1998. Why women are less likely than men to commit suicide. Compr. Psychiatry 39, 165–175.
11. Henderson, J.P. Mellin, C. Patel, F. 2005. Suicide—a statistical analysis by age, sex and method. J. Clin. Forensic Med. 12, 305–309
12. Massimiliano Beghi, Cesare Giuseppe Cerri, Cesare Maria Cornaggia, Francesca Febbo, Anita Mollica, Giuseppe Berardino, Daniele Piscitelli, Emanuela Resta, Giancarlo Logroscino, Antonio Daniele, Mario Altamura, Antonello Bellomo, Francesco Panza, Madia Lozupone. Suicidal behaviour in older age: A systematic review of risk factors associated to suicide attempts and completed suicides Neurosci Biobehav Rev. 2021, 127:193-211.
13. Richard D Semba. Treatment of depression: time to consider folic acid and vitamin B12 J Psychopharmacol. 2005 ,19(1):59-65.
14. Kathleen Mikkelsen, Lily Stojanovska, Vasso Apostolopoulos. The Effects of Vitamin B in Depression, Curr Med Chem. 2016;23(38):4317-4337.
15. David T Field, Rebekah O Cracknell, Jessica R Eastwood, Peter Scarfe, Claire M Williams, Ying Zheng, Teresa Tavassoli High-dose Vitamin B6 supplementation reduces anxiety and strengthens visual surround suppression, Hum Psychopharmacol. 2022, 37(6):e2852.
16. E H Reynolds. The neurology of folic acid deficiency, Handb Clin Neurol. 2014;120:927-43.
17. Chunmei Geng, Abdul Sami Shaikh[2], Wenxiu Han, Dan Chen, Yujin Guo, Pei Jiang Vitamin D and depression: mechanisms, determination and application,Asia Pac J Clin Nutr. 2019;28(4):689-694.

18. Gordon B Parker, Heather Brotchie, Rebecca K Graham. Vitamin D and depression J Affect Disord. 2017 Jan 15;208:56-61.
19. Gleicilaine A S Casseb, Manuella P Kaster, Ana Lúcia S Rodrigues Potential Role of Vitamin D for the Management of Depression and Anxiety, CNS Drugs. 2019,33(7):619-637.
20. Elisa J de Koning, Paul Lips, Brenda W J H Penninx, Petra J M Elders, Annemieke C Heijboer, Martin den Heijer, Pierre M Bet, Harm W J van Marwijk, Natasja M van Schoor. Vitamin D supplementation for the prevention of depression and poor physical function in older persons: the D-Vitaal study, a randomized clinical trial, Am J Clin Nutr. 2019, 1;110(5):1119-1130.
21. Nithila Mariam Roy, Lara Al-Harthi, Neela Sampat, Rawan Al-Mujaini, Sangeetha Mahadevan, Samir Al Adawi, Musthafa Mohamed Essa, Lyutha Al Subhi, Buthaina Al-Balushi, M Walid Qoronfleh Impact of vitamin D on neurocognitive function in dementia, depression, schizophrenia and ADHD, Front Biosci (Landmark Ed). 2021, 1;26(3):566-611.

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The Evaluation of the Burden and Burnout Levels of the Caregivers of the Inpatients in Palliative Care

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ABSTRACT

The study was conducted to evaluate the care burden and burnout levels of caregivers for patients hospitalized in palliative care. This descriptive study was conducted with 76 caregivers who were hospitalized in the palliative care services of a university and state hospital between 02.12.2019 and 02.06.2022 in Turkey. After obtaining the permissions of the ethics committee and the institution, the data were collected with the Descriptive Characteristics Form, Palliative Performance Scale, Caregivers Burden Inventory, and Maslach Burnout Inventory. The total score of the Caregivers Burden Inventory was 50.31±15.37, sub-dimensions of time-dependency burden, developmental burden, physical burden, social burden, and emotional burden scores were 18.30±3.23, 10.94±6.03, 13.54±5.99, 4.09±4.68, and 3.42±3.89, respectively. The Maslach Burnout Inventory sub-dimensions were emotional exhaustion, depersonalization, and personal accomplishment, with mean scores of 24.78±10.33, 11.59±4.20, and 28.64±5.67, respectively. The mean Palliative Performance Scale score of the patients was 32.76±16.86. As the care burden of caregivers increased, so did their exhaustion scores. Caregivers had moderate care burdens, high time dependency and physical burdens, high emotional exhaustion, and low personal accomplishment burnout. All patients who were cared for were bedridden. The presence of incontinence in the patient affected the time dependency care burden of the caregivers, and the presence of chronic disease in the caregiver and living with the patient also affected the caregivers' emotional exhaustion. These results show that studies must be conducted to develop multidisciplinary interventions to reduce caregivers' care burden and burnout.

Keywords: Palliative care, caregiver, care burden, burnout

Palyatif Bakımda Yatan Hastalara Bakım Verenlerin Yük ve Tükenmişlik Düzeylerinin Değerlendirilmesi

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ÖZ

Araştırma palyatif bakımda yatan hastalara bakım verenlerin bakım yükü ve tükenmişlik düzeylerini değerlendirmek amacıyla yapılmıştır. Tanımlayıcı tipte olan bu çalışma, Türkiye'de 02.12.2019 ile 02.06.2022 tarihleri arasında bir üniversite ve devlet hastanesinin palyatif bakım servislerinde yatan 76 bakım veren ile gerçekleştirildi. Etik kurul ve kurum izinleri alındıktan sonra Tanımlayıcı Özellikler Formu, Palyatif Performans Ölçeği, Bakım Veren Yük Envanteri ve Maslach Tükenmişlik Envanteri ile veriler toplandı. Bakım Verenlerin Yükü Envanterinin toplam puanı 50,31±15,37, zamana bağımlılık yükü, gelişimsel yük, fiziksel yük, sosyal yük ve duygusal yük alt boyutları puanları ise sırasıyla 18,30±3,23, 10,94±6,03, 13,54±5,99, 4,09±4,68 ve 3,42±3,89olarak belirlendi. Maslach Tükenmişlik Envanteri alt boyutları duygusal tükenme, duyarsızlaşma ve kişisel başarı olup ortalama puanları sırasıyla 24,78±10,33, 11,59±4,20 ve 28,64±5,67'dir. Hastaların Palyatif Performans Ölçeği puanı ortalaması 32,76±16,86 idi. Bakım verenlerin bakım yükü arttıkça tükenmişlik puanları da artmaktadır. Bakım verenlerin orta d91recede bakım yükü, yüksek zamana bağımlılık ve fiziksel yük, yüksek duygusal tükenme ve düşük kişisel başarı tükenmişliği vardı. Tedavi gören hastaların tamamı yatalak durumdaydı. Hastada inkontinans varlığı bakım verenlerin zamana bağlı bakım yükünü etkilediği gibi, bakım verende kronik hastalık varlığı ve hastayla birlikte yaşama da bakım verenlerin duygusal tükenmesini etkilemiştir. Bu sonuçlar bakım verenlerin bakım yükünü ve tükenmişliğini azaltmaya yönelik multidisipliner müdahalelerin geliştirilmesine yönelik çalışmaların yapılması gerektiğini göstermektedir.

Anahtar sözcükler: Palyatif bakım, bakım veren, bakım yükü, tükenmişlik

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Introduction

The palliative approach improves the quality of life of patients (children and adults) and their families facing problems associated with life-threatening diseases, prevents and alleviates pain through early detection, accurate assessment, and treatment of pain and other physical, psychosocial, or mental problems[1].

Palliative care is needed for a wide variety of diseases around the world. An estimated 56.8 million people require palliative care each year, of which 25.7 million are in the last year of life. Only approximately 14% of people currently in need of palliative care receive it worldwide [1-3]. Palliative care services were put into service in 2010 in Turkey, and today, they continue to be provided by 297 health facilities with 3,899 beds in 79 provinces [4].

Caregiving means the process of undertaking care delivery activities and responsibilities. A caregiver is defined as an individual (i.e., a spouse, partner, family member, friend, or neighbor) who provides unpaid care to others in their daily activities and/or illness-related processes [5]. The caregiver must learn how to deal with a patient. In this process, the caregiver usually begins to feel a significant caregiver burden and is at risk of caregiver burnout[6]. In a study conducted by Gerain (2019), it was found that there is a relationship between caregiver stress, burden, and burnout [7]. The burden is defined as negative subjective and objective consequences such as psychological distress, physical health problems, economic and social problems, deterioration of family relationships, and loss of control. The caregiver feels obliged to provide the patient's treatment, personal care, and psychosocial support[1,6]. Perpiñá-Galvañ et al. (2019) reported that anxiety is a significant problem in primary family caregivers of palliative care patients and there are signs of an intense burden on caregivers [8]. Caregiver burden also causes negative impacts on the emotional, social, financial, physical, and spiritual functioning of the caregiver [9]. Also, in burnout, the caregiver's physical health or emotional well-being is negatively affected due to the stress associated with caring for someone with care needs. Typically, burnout occurs when the caregiver does not receive adequate support or when the caregiver is overworked with too many tasks and responsibilities [9]. Also, burnout is a three-dimensional syndrome occurring in response to chronic stress [10]. Caregiver burnout can manifest in 3 ways feeling tired, not having the strength to continue giving care, and/or starting to withdraw from regular caregiving [11,12]. When outcomes related to caregiving are evaluated, especially the jobs and potential burdens that are likely to result in burnout for caregivers, which will affect both the caregiver and the care recipient, must be taken into account [13,14]. The care and treatment of patients in palliative care is a very difficult process in which the burden and burnout levels of caregivers can be affected at various levels. In the literature review, no study was detected in which the burden of caregivers was evaluated with the Caregiver Burden Inventory [15]. By associating it with the palliative performance scale score of patients hospitalized in palliative care, and their burnout was examined. In this regard, the study was conducted to contribute to the development of interventions to meet the needs of patients in palliative care by evaluating the care burden and burnout levels of caregivers.

Material Method

All procedures performed in procedures involving human participants were in accordance with the ethical standards of the institutional and/or national study committee. Before starting the study, approval was obtained from the Non-Interventional Clinical Study Ethics Committee of a university (Sivas Cumhuriyet University, Decision No: 2019-11/19). Written permission was obtained from the university hospital administration (93596471-774.99-E.32863) and Sivas Provincial Health Directorate (76728045-799-2557), where the implementation was made.

After selecting the eligible participants who agreed to participate in the study, the researchers were introduced to them, and the objectives of the study were explained to the participants. The participants were ensured that their information would remain confidential, and they provided informed consent. The study was conducted following the principles of the Declaration of Helsinki.

Study design and sample

This descriptive study was conducted with 76 caregivers of patients who were hospitalized in palliative care services of a university (33) and state (43) hospital between 02.12.2019 and 02.06.2022 in Turkey. In the study, no sample selection was made in the population, and all caregivers who volunteered to participate in the study and met the research criteria were included in the sample. The fact that the study was conducted during the COVID-19 pandemic and the length of hospitalization in palliative care caused the sample size to be limited.

The caregivers who were primarily responsible for the care of the patient in the hospital and at home, 18 years of age and older, paid or unpaid care, and literate, non-communicative caregivers were included in the study. Interviews were conducted with those who cared for the patient for longer in patients with more than one caregiver. The researchers provided them with an explanation of the study. Written informed consent was obtained from all.

Measures

The data were collected with the Descriptive Characteristics Form, Palliative Performance Scale (PPS), Caregiver Burden Inventory (CBI), and Maslach Burnout Inventory (MBI).

1. Descriptive Characteristics Form

In this form, which was created by researchers in line with the relevant literature data [6, 8, 9, 13, 14], there are 21 questions to learn information about the individuals the caregivers cared for. The form included 14 questions to determine the introductory characteristics of caregivers. Also, there were 7 questions to determine the introductory characteristics of the caregivers that may affect the burden of caregivers and burnout.

2. Palliative Performance Scale

Anderson et al. reported the development and trial use of the Palliative Performance Scale (PPS) in 1996 as a new tool for measuring functional status in palliative care [16]. The Turkish validity and reliability of the PPS were conducted by Oğuz et al. (2021). The score is derived from the assessment of 5 domains ambulation, activity, and evidence of disease, self-care, intake, and level of consciousness. The PPS is divided into 11 levels, from PPS 0% to PPS 100%, in 10% increments, a patient at PPS 0% is dead and at 100% is ambulatory and healthy [17].

3. Caregiver Burden Inventory

This is an inventory developed by Novak and Guest (1989) to quantify the impact of caregiving on caregivers [15]. The Caregiver Burden Inventory (CBI) includes five dimensions, namely time-dependent (T/dep-B), developmental (Dev-B), physical (Phys-B), social (Soc-B), and emotional burdens (Emot-B). It is a 5-level Likert-type scale. The score is between 0 and 100 (0 to 20 in each dimension) [15]. A higher score indicates a higher burden. The form was adapted for Turkish society [18]. The CBI Cronbach alpha value was 0.94, 0.93 for T/dep-B, 0.94 for Dev-B, 0.94 for Phys-B, 0.82 for Soc-B, 0.94 for Emot-B18. In this study, Cronbach's alpha = 0.86 for these five dimensions (0.873, 0.862, 0.891, 0.767, 0.750, respectively).

4. Maslach Burnout Inventory

This 22-item tool was developed by Maslach10 and adapted for Turkish people with validity and reliability studies conducted by Ergin (1992) [19] and Çam (1996) [20]. This five-point Likert-type scale evaluates three dimensions of burnout. These are emotional exhaustion (EE), depersonalization (D), and personal accomplishment (PA). The inventory of the EE subscale contains 9 items, the D subscale contains 5 items and the PA subscale has 8 items. High scores on the EE and D subscales but low scores on the PA subscale are considered burnout19. Ergin (1992) found Cronbach's alpha reliability coefficients for three dimensions to be 0.83 for EE, 0.65 for D, and 0.72 for a sense of PA [19]. The Cronbach's alpha was found to be 0.916 for EE, 0.815 for D, and 0.727 for PA in this study.

Statistical analysis

The data collected in this study were analyzed by using SPSS version 22.0. Frequencies, percentages, and mean values were used in the descriptive analyses. The normality of the distributions of the data was assessed by using the Kolmogorov–Smirnov test. Since the data did not meet the parametric test conditions, the Mann–Whitney U test was used for two independent groups, and the Kruskal–Wallis test was used for more than two independent groups. We also analyzed the Spearman rank correlation coefficient test for continuous variables to identify factors that were significantly associated with caregiver burden burnout and the patients' Palliative Performance Scale. Simple regression investigated predictors of caregiver burden and burnout. The level of statistical significance was taken as 0.05.

Results

The mean age of the caregivers was 53.86±14.72 (Min:21, Max:82), and 72.4% of them were women. 81% of the participants were married, 82.9% had children, 75% did not work in any job, and 17.1% perceived their income as good. Also, 52.6% of caregivers had a chronic disease (Table 1).

A total of 26.3% of the caregivers lived with the spouse of the patient and 65.8% lived with their patients. When giving care to their patients, 71.1% of the participants received support from their

siblings (64.8%). Of the patient 85.5% were elderly, 50% had behavioral problems and 84.2% had

incontinence. In addition to these, the average PPS score of the patients was 32.76±16.86 (Table 2).

Table 1. The descriptive characteristics of the caregivers of the patients

	n (%)
The hospital where the patient is hospitalized	
University hospital	33 (43.4)
Public Hospital	43 (56.6)
Mean age $\bar{x}$: 53.86±14.72 (Min:21, Maks:82)	
40 years and under	14 (18.4)
41- 64 years	43 (56.6)
65 years and older	19 (25.0)
Gender	
Female	55 (72.4)
Male	21 (27.6)
Education level	
Illiterate	9 (11.8)
Literate with no formal degree	8 (10.5)
Primary-secondary school	38 (50.0)
High school	13 (17.1)
University	8 (10.5)
Marital status	
Married	62 (81.6)
Single	14 (18.4)
Having Children	
Yes	63 (82.9)
No	13 (17.1)
Employment status	
Working	19 (25.0)
Not working	57 (75.0)
Income level	
High income	13 (17.1)
Middle income	55 (72.4)
Low income	8 (10.5)
Chronic disease	
Yes	40 (52.6)
No	36 (47.4)

The CBI sub-dimensions of the caregivers were T/dep-B, Dev-B, Phys-B, Soc-B, and Emot-B. and their mean scores were 18.30±3.23, 10.94±6.03, 13.54±5.99, 4.09±4.68 and 3.42±3.89, respectively. The CBI total score was 50.31±15.37. The MBI sub-dimensions were EE, D and PA with mean scores of 24.78±10.33, 11.59±4.20, and 28.64±5.67, respectively (Table 3).

The difference between the Dev-B among the caregivers of illiterate ($p<0.05$) and chronic disease ($p<0.001$) and others was high and statistically significant. Elderly ($p<0.05$), unemployed ($p<0.05$), and caregivers with chronic disease ($p<0.001$) had statistically significantly higher Phys-B. The Soc-B of the male caregivers was high and the difference between them and the others was statistically significant ($p<0.05$). The EE of caregivers who were illiterate ($p<0.05$), unemployed ($p<0.05$), poor income status ($p<0.05$), and chronic disease ($p<0.001$) were statistically and significantly higher. The total score of the CBI of those with chronic diseases is also significantly higher than the others ($p<0.001$) (Table 4).

Table 2. The caring characteristics of the caregivers of the patients

	n (%)
Relationship with patient	
Spouse	20 (26.3)
Children	43 (56.6)
Non-familial caregivers (paid caregiver)	8 (10.5)
Others (Parent, sibling, grandchild, bride)	5 (6.6)
Caregiving Time	
1 year and below	61 (80.3)
Over 1 year	15 (19.7)
Living with the patient	
Yes	50 (65.8)
No	26 (34.2)
Status of the person supporting the care	
Yes	54 (71.1)
No	22 (28.9)
Relationship with patient of the individual who supports the care to the patient (n=54)	
Child	12 (22.2)
Brother/Sister	35 (64.8)
Other (parent, grandchild, bride, uncle)	7 (13.0)
The status of receiving education for care	
Yes	58 (76.3)
No	18 (23.7)
Patient age group $\bar{x}$: 75.28±10.76 (Min:40, Maks:93)	
40-64 years	11 (14.5)
65 years and above	65 (85.5)
Patient behavioral problems (verbal-physical attack, agitation, etc.)	
Yes	38 (50.0)
No	38 (50.0)
Patient incontinence (urine/ stool) status	
Yes	64 (84.2)
No	12 (15.8)
Patient pychiatric disease (dementia, depression) status	
Yes	28 (36.8)
No	48 (63.2)
Patient neurodegenerative disease (Alzheimer, Parkinson) status	
Yes	31 (40.8)
No	45 (59.2)
Palliative Performance Scale $\bar{x}$: 32.76±16.86 (Min:10, Maks:70)	

The differences between T/dep-B the caregivers of the patients who received training on care (p<0.05), who had behavioral problems (p<0.001) and who had incontinence (p<0.001) were found to be higher than the others, and the differences between them were statistically significant. The total burdens (p<0.05), Dev-B, and Phys-B (p<0.001) of the caregivers living with their patients were significantly higher. The Phys-B of the caregivers who were the spouses of the patients and the children who supported the care was higher than the others, and the difference between them was statistically significant (p<0.001). Soc-B was higher in caregivers of neurodegenerative patients compared to others (p<0.001). The caregivers of patients who had behavioral problems and neurodegenerative diseases had higher Emot-B and the difference between them was statistically

significant ($p<0.05$). Among the caregivers, the EE of the patient's relatives (parent, sibling, grandchild, daughter-in-law) ($p<0.001$), children supporting the care ($p<0.05$), and caregivers living with the patient ($p<0.001$) were found to be statistically and significantly higher. The D levels of the caregivers who lived with their patients and were trained for care were high and the difference between them was found to be statistically significant ($p<0.05$). It was also found that the levels of burnout due to PA of caregivers who gave care to inpatients in palliative care were statistically significantly higher than the others ($p<0.001$) (Table 5).

In the present study, a negative, moderate, and highly significant relationship was detected between T/dep-B and PPS (r=-0.592, p≤0.001). Also, a high level and positive correlation was detected between caregivers' total CBI score and MBI sub-dimensions EE (r=0.758, p≤0.001) and D (r=0.868, p≤0.001), and a moderate, high, and significant negative relationship was detected with PA (r=-0.364, p≤0.001). A negative, moderate and highly significant relationship was detected between the incontinence of the patient being cared for and T/dep-B (r=-591, p≤0.001) in the study. It was also found that caregivers with chronic disease (r=-378, p≤0.001) and living with their patients (r=-347, p≤0.001) had a negative, moderately highly significant relationship with EE.

Table 3. The mean scores of the Caregivers Burden Inventory and the Maslach Burnout Inventory of caregivers of patients

Scales	Scale sub-dimensions/ total score	$\bar{X}$±SD	Median	Min- Maks.	Point Range
Caregiver Burden Inventory	Time-Dependent Burden	18.30±3.23	20.00	1-20	0-20
	Developmental Burden	10.94±6.03	12.00	0-20	0-20
	Physical Burden	13.54±5.99	13.75	0-20	0-20
	Social Burden	4.09±4.68	3.00	0-20	0-20
	Emotional Burden	3.42±3.89	2.00	0-20	0-20
	Caregiver Burden Inventory	**50.31±15.37**	**51.00**	**20-83**	**0-100**
Maslach Burnout Inventory	Emotional Exhaustion	24.78±10.33	23.00	9-43	9-45
	Depersonalization	11.59±4.20	11.50	3-21	1-25
	Personal Accomplishment	28.64±5.67	29.00	13-40	1-40

It was shown that the T/dep-B of the caregivers could explain 34.9% of the presence of incontinence in the patient being cared for. The presence of incontinence in the caregiver affected the T/dep-B of the caregivers significantly by 59.2%. It was also shown that the EE of the caregivers participating in

the study can explain 22.9% of the caregiver's chronic disease and living with their patients. The presence of chronic disease and living with their patients significantly affected the EE of the caregivers by 47.9% (Table 6).

Table 4. The mean scores of the Caregivers Burden Inventory and Maslach Burnout Inventory according to the descriptive characteristics of caregivers of patients

Scale / Descriptive Features	Caregiver Burden Inventory					Maslach Burnout Inventory		
	Time-Dependent Burden	**Developmental Burden**	**Physical Burden**	**Social Burden**	**Emotional Burden**	**Emotional Exhaustion**	**Deperson-alization**	**Personal Accomplis-hment**
Age Groups								
40 years and below	17.64±2.76	11.35±5.81	10.26±5.61	4.78±4.13	4.50±5.30	23.35±9.86	11.64±4.92	28.85±7.50
41- 64 years	18.86±2.18	9.83±6.46	13.25±5.98	3.72±4.80	2.97±3.34	22.74±10.26	10.91±3.76	28.8±5.43
65 years and above	17.52±5.26	13.15±4.66	16.63±4.97	4.42±9.92	3.63±3.94	28.18±10.16	12.46±4.35	28.33±5.08
KW	5.165	0.543	**8.106**	1.237	1.400	4.428	1.985	0.706
p	0.577	0.761	**0.017***	0.538	0.496	0.109	0.370	0.702
Gender								
Female	18.38±2.65	11.05±5.86	13.93±5.86	3.41±4.43	3.29±3.26	24.80±10.30	11.31±4.09	28.58±5.62
Male	18.09±4.49	10.66±6.62	12.53±6.36	5.85±4.95	3.76±4.30	24.76±10.69	12.33±4.50	28.80±5.92
Z	-0.685	-0.239	-0.838	**-2.094**	-0.208	-0.110	-1.100	-0.547
p	0.745	0.811	0.402	**0.036***	0.835	0.912	0.272	0.584
Education level								
Illiterate	17.55±4.12	16.88±4.56	16.19±5.45	7.44±7.35	6.22±5.58	34.33±9.88	15.16±4.44	27.55±6.82
Literate with no formal degree	18.75±3.57	10.75±6.47	15.31±6.70	3.25±3.37	3.87±4.38	31.37±10.91	12.75±4.88	25.37±5.09
Primary-secondary school	18.15±3.57	9.68±5.92	13.59±5.85	3.60±4.30	2.97±3.34	22.76±9.22	10.90±3.56	28.94±5.13
High school	18.53±2.69	11±5.43	12.59±5.60	3.92±4.76	3.69±4.15	23.76±10.90	11.38±4.67	29.84±6.29
University	19±1.77	10.37±5.87	10.15±6.62	3.75±2.86	1.5±1.92	18.75±5.36	10.06±3.94	29.75±6.31
KW	0.702	**10.595**	5.837	2.139	4.788	**13.240**	7.759	3.884
p	0.951	**0.031***	0.211	0.710	0.309	**0.010***	0.100	0.421
Employment status								
Working	18.78±1.98	10.10±6.53	10.65±6.95	3.89±4.85	3.10±3.95	19.52±8.90	10.76±4.69	30.63±5.87
Not working	18.14±3.55	11.22±5.89	14.51±5.37	4.15±4.66	3.52±3.91	26.54±10.25	11.87±4.03	27.98±5.49
Z	-0.541	-0.607	**-2.126**	-0.431	-0.705	**-2.533**	-0.835	-1.575
p	0.588	0.543	**0.033***	0.666	0.481	**0.011***	0.404	0.115
Income level								
High income	18.76±3.13	11.46±5.66	11.63±6.68	3.61±4.07	2.53±2.93	21.46±10.38	11.15±3.92	30.61±4.97
Middle income	18.27±3.30	10.45±5.91	13.74±5.86	3.70±4.34	3.45±3.79	24.34±9.98	11.43±4.08	28.47±5.51
Low income	17.75±3.24	13.5±7.48	15.31±5.69	7.5±6.78	4.62±5.80	33.25±9.40	13.43±5.49	26.62±7.44
KW	1.188	1.790	1.838	2.720	0.744	**6.456**	1.942	1.471
p	0.552	0.408	0.398	0.256	0.689	**0.039***	0.378	0.479
Chronic disease								
Yes	18.17±2.99	13.27±4.70	15.77±4.71	4.3±4.99	3.95±4.05	28.47±10.14	12.78±4.05	27.3±5.48
No	18.44±3.52	8.36±6.35	11.07±6.35	3.86±4.36	2.83±3.68	20.69±9.03	10.27±4.02	30.13±5.57
Z	-0.680	**-3.229**	**-3.371**	-0.379	-1.617	**-3.258**	-2.584	**-2.315**
p	0.496	**0.001****	**0.001****	0.704	0.105	**0.001****	0.009	**0.020***

Abbreviations: Z, Mann Whitney U**;** KW, Kruskal Wallis

*p<0.05, **p<0.001

Table 5. The mean scores of the Caregivers Burden Inventory and Maslach Burnout Inventory according to the caregiver characteristics of the caregivers of patients

Scale / Characteristics of the caregivers	Caregiver Burden Inventory					Maslach Burnout Inventory		
	Time-Dependent Burden	Developmental Burden	Physical Burden	Social Burden	Emotional Burden	Emotional Exhaustion	Deperson-alization	Personal Accomplish-ment
Relationship with patient								
Spouse	17.35±4.95	14.05±5.12	16.98±4.74	4.3±6.00	3.45±3.74	31.5±8.34	12.7±4.27	28±4.41
Children	18.62±2.38	9.65±5.87	12.5±5.60	4.72±4.366	3.72±4.06	22.30±10.09	11.05±3.89	28.02±6.01
Non-familial caregivers	18.75±2.05	9.37±6.41	10±7.41	1.12±2.100	1±2.13	17.12±5.64	10±4.90	34.12±3.31
Others (Parent, sibling, grandchild, bride)	18.6±2.60	12.2±7.15	14.5±6.64	2.6±2.607	4.6±4.77	31.6±9.01	14.4±4.49	27.8±6.61
KW	0.381	7.682	**12.67**	6.620	5.366	**16.99**	4.894	**9.932**
p	0.944	0.053	**0.005****	0.085	0.146	**0.001****	0.179	**0.019***
Living with the patient								
Yes	17.92±3.72	12.22±6.12	14.87±5.43	4.18±4.88	3.84±3.97	27.36±10.70	12.44±4.19	28.66±5.70
No	19.03±1.84	8.5±5.14	11.00±6.31	3.92±4.34	2.61±3.69	19.84±7.59	9.98±3.81	28.61±5.70
Z	-1.064	**-2.608**	**-2.692**	-0.016	-1.494	**-2.931**	**-2.500**	-0.164
p	0.287	**0.009****	**0.007****	0.986	0.134	**0.003****	**0.012***	0.869
Relationship with patient of the individual who supports the care to the patient (n=54)								
Child	18.91±1.97	13.25±6.19	16.87±5.57	3.08±4.56	4±4.13	31.41±9.51	12.41±5.17	27.75±4.51
Brother/Sister	17.97±4.15	9.65±6.36	12.86±5.23	4.2±4.17	2.71±3.23	22.97±10.11	10.88±3.56	28.94±5.14
Other (parent, grandchild, bride, uncle)	18.28±2.21	9.42±5.50	8.39±5.57	3.85±2.79	2.71±3.45	19.42±9.28	9.78±3.92	27.14±7.79
KW	0.276	3.480	**10.497**	1.638	1.014	**7.235**	2.332	1.462
p	0.871	0.175	**0.005****	0.440	0.602	**0.026***	0.311	0.481
The status of receiving education for care								
Yes	18.55±3.34	11.29±6.36	14.21±5.97	3.91±4.75	3.5±3.91	25.43±10.69	12.19±4.12	28.60±4.94
No	17.5±2.79	9.83±4.82	11.38±5.70	4.66±4.52	3.16±3.94	22.72±9.07	9.66±3.98	28.77±7.72
Z	**-2.353**	-1.170	**-2.017**	-0.966	-0.287	-0.874	**-2.337**	-0.355
p=	**0.018***	0.241	**0.043***	0.333	0.774	0.381	**0.019***	0.722
Patient behavioral problems (verbal-physical attack, agitation, etc.)								
Yes	19.21±1.86	10.52±5.90	14.26±5.83	3.44±3.86	4.05±3.80	24.34±10.27	12.10±4.14	27.15±6.13
No	17.39±4.01	11.36±6.22	12.83±6.14	4.73±5.35	2.78±3.93	25.23±10.52	11.09±4.26	30.13±4.79
Z	**-2.578**	-0.479	-1.092	-0.805	**-1.991**	-0.337	-0.884	-1.895
p	**0.009****	0.631	0.274	0.420	**0.046***	0.735	0.376	0.058
Patient incontinence (urine/ stool) status								
Yes	19.125±1.64	10.54±6.06	13.89±6.10	3.90±4.94	3.64±3.75	24.23±10.10	11.65±4.29	28.59±5.46
No	13.91±5.56	13.08±5.66	11.68±5.23	5.08±2.90	2.25±4.61	27.75±11.52	11.29±3.89	28.91±6.94
Z	**-3.939**	-1.307	-1.440	-1.843	-1.828	-0.912	-0.413	-0.235
p	**0.001****	0.191	0.149	0.065	0.067	0.361	0.679	0.813
Patient neurodegenerative disease (Alzheimer, Parkinson) status								
Yes	18.61±2.48	11.25±5.25	13.00±6.19	5.96±5.37±	4.25±3.68	23.54±9.95	11.90±4.03	29.03±5.64
No	18.08±3.67	10.73±6.57	13.92±5.89	2.8±3.67	2.84±3.97	25.64±10.62	11.38±4.35	28.37±5.73
Z	-0.061	-0.084	-0.692	**-2.839**	**-2.080**	-0.835	-0.635	-0.556
p	0.951	0.932	-0.692	**0.004****	**0.037***	0.403	0.525	0.578

Abbreviations: Z, Mann Whitney U**;** KW, Kruskal Wallis
*p<0.05, **p<0.001

Table 6. The results of the Caregiver Burden Inventory and Maslach Burnout Inventory regression analysis

Depend Variable Time-Dependent Burden							
Independ Variable	**B**	**SE**	**Beta**	**t**	**p**	**95% CI for β**	
						Lower Limit	**Upper Limit**
Constant	24.33	1.004	-0.591	24.226	0.001*	22.332	26.335
Patient incontinence (urine/ stool) status	-5.208	0.827		-6.295	0.001*	-6.857	-3.560
R:0.591; R2:0.349; F:(39.626) ;p:0.001; Durbin Watson:1.777							
*p< 0.001							
Depend Variable Emotional Exhaustion							
Independ Variable	**B**	**SE**	**Beta**	**t**	**p**	**95% CI for β**	
						Lower Limit	**Lower Limit**
Constant	43.550	4.161		10.466	0.001*	35.256	51.843
Caregiver chronic disease status	-6436	2.250	-0.297	-2.861	0.006*	-10.919	-1.952
Living with the patient	-6.869	2.137	-0.334	-3.214	0.002*	-11.129	-2.609
R:0.479; R2:0.229; F:(10.868) ;p:0.001							
*p<0 .001							

Discussion

Problems that are associated with life-threatening diseases affect both patients and caregivers at

various levels. Palliative care services provide services to patients and caregivers to minimize these impacts and prevent and alleviate pain and suffering. Caregiving can turn into a care burden and burnout in caregivers over time. Accordingly, the findings of the study and the care burden and burnout levels of caregivers are discussed in the following section within the current literature.

In the present study, caregivers were found to have a moderate burden of care, a high level of T/dep-B, EE, and low PA burnout. In previous studies conducted with patients hospitalized in palliative care, it was found that

caregivers experience a care burden [8, 21-23]. Similarly, Saraçoglu et al. (2022) [24] and Egici et al. (2019) [25] reported in their study that as the burden of caregivers increased, so did their burnout scores, and their PA- related burnout was low. Personal achievement encompasses positive dimensions of the helping experience, emphasizing that the caregiver can gain a sense of satisfaction and find meaning in the care work [26]. In the context of burnout, the tendency to increase this positive sense of achievement is thought to be related to the caregivers' efforts to give the best care [8, 21-24]. During the study process, almost all of the participants used the expression "I do my best while giving care". In previous studies, the different levels of burden and burnout of caregivers were associated with the patient groups and caregivers' characteristics, cultural, social, and support resources [8, 21-23]. These results also show that as caregivers' burden of care increased, their burnout also increased.

A low PPS score causes bed dependence, meeting basic physiological needs in bed, and the patient's need for more care, which affects the caregiver's care intensity, time allocated for care, caregiver burden, and burnout. All patients who were cared for in this study were bedridden according to their PPS scores. The caregivers of the bedridden and incontinence patients had a high time dependency burden. According to Ahmad Zubaidi et al. (2020), in the Eastern Cooperative Oncology Group (ECOG) performance scale, 55.4% of patients were bedridden and caregivers experienced a burden of care [22]. Similarly, Guerriere et al. (2016) reported that the burden of caregivers of patients with low PPS scores was higher [27].

It was also found that the total burden of caregivers with chronic diseases was higher. For caregivers who were illiterate, unemployed, low-income, and with chronic diseases the emotional exhaustion was higher, too. In the literature review, it was reported that the burden of care was higher because those with higher education levels were more conscious [22, 25, 28, 29]. According to Egici et al. (2019), however, no relationship was detected between caregivers' gender, education, degree of closeness, and burden of care and burnout [25]. The high burden of care in individuals who had low educational status was associated with the feeling of uncertainty because of not knowing the progress of their patients in the care process and giving more weight to care. According to Saraçoglu et al. (2022), caregivers who had low- income levels had high burdens and burnout [24]. Although the cost of treatment and care for critically ill individuals is high, it can be considered that low-income levels may play roles in the caregivers' feeling of care burden and burnout. In previous studies, it was found that caregivers with health problems or chronic diseases had a high burden of care [8, 28, 29] and EE [25]. Finding similar results with the literature is considered to be an indication that individuals with chronic diseases affect the care burden and emotional exhaustion while struggling and managing their health problems, as well as taking care of the patients.

The total burden of caregivers living with their patients and EE, the Phys-B of the children who were the spouses of the patients and supported the care, the Emot-B of the caregivers of the patients who had behavioral problems, and the D of the caregivers were found to be high. Studies reported that the risk of developing a care burden was higher in caregivers who were the spouses or lovers of the patients [29, 30]. Alsirafy et al. (2021) on the other hand, found that the degree of closeness of the caregivers to the patient and living with the patient did not affect their care burden [21]. In studies conducted on burnout, it was found that caregivers experienced more emotional exhaustion, less depersonalization, and lower personal accomplishment than non-caregivers [31]. When additional duties are given to caregivers, their care burden, EE, and D were found to be higher than other caregivers [25]. In the study conducted by Hiyoshi-Taniguchi, Becker, and Kinoshita (2018), it was found that caregivers experienced higher burnout when faced with agitation/aggression, irritability, abnormal motor behavior, and hallucinations [32]. When evaluating caregiver care burden and burnout, both patient and caregiver characteristics that might affect caregivers must be investigated and measures must be taken to prevent or minimize negative impacts.

LIMITATIONS

The long-term hospitalization of patients in palliative care services and the coinciding of the data collection process with the COVID-19 pandemic caused a limitation in the number of samples. Research results are limited to the sample studied, cannot be generalized. In addition, the limitations of the research can be stated as the fact that the research was conducted only in Sivas province.

CONCLUSION

As the burden of caregivers increased, so did their exhaustion levels. Caregivers have a moderate care burden, high time dependency and physical burdens, high emotional exhaustion, and low personal accomplishment burnout. All patients who were cared for were bedridden. The presence of incontinence in the patient affected the time dependency burden of the caregivers, and the presence of chronic disease in the caregiver and living with the patient also affected the caregivers' emotional exhaustion. These results may indicate the need for studies to develop multidisciplinary approaches to reduce caregivers' care burden and burnout.

References

1. WHO. Palliative Care https://www.who.int/news-room/fact-sheets/detail/palliative-care
2. The Worldwide Hospice Palliative Care Alliance (WHPCA). Global Atlas of Palliative Care, 2020, 2. Edt.
3. Family Caregiver Alliance. © 2016 Family Caregiver Alliance
4. CDC. Caregiving for Family and Friends — A Public Health Issue
5. Hudson P, Payne S. Family caregivers and palliative care: current status and agenda for the future. J Palliat Med. 2011; 14(7):864-869.
6. Gérain P, Zech E. Informal Caregiver Burnout? Development of a Theoretical Framework to Understand the Impact of Caregiving. Front Psychol. 2019;10:1748.
7. Perpiñá-Galvañ J, Orts-Beneito N, Fernández-Alcántara M, García-Sanjuán S, García-Caro MP, Cabañero-Martínez MJ. Level of Burden and Health-Related Quality of Life in Caregivers of Palliative Care Patients. Int J Environ Res Public Health. 2019;16(23):4806.
8. Hategan A, Bourgeois JA, Cheng T, Young J. Caregiver Burnout. In: Geriatric Psychiatry Study Guide: Mastering the Competencies, Springer International Publishing, 1st ed. 2018.
9. Maslach C, Jackson S. E, Leiter MP. Maslach burnout inventory, 3rd ed. Consulting Psychologists Press, 1996.
10. Burn-out an “occupational phenomenon”: International Classification of Diseases. Geneva: WHO, 2020. [cited 2022 July 10].
11. Recognizing Caregiver Burnout. Geneva: WHO, 2020.
12. Alam S, Hannon B, Zimmermann C. Palliative Care for Family Caregivers. J Clin Oncol. 2020; 38(9):926-936.
13. Berry LL, Dalwadi SM, Jacobson JO. Supporting the Supporters: What Family Caregivers Need to Care for a Loved One with Cancer. J Oncol Pract. 2017; 13(1):35-41.
14. Novak M, Guest C. Application of a multidimensional caregiver burden inventory. Gerontologist. 1989;29(6):798-803.
15. Anderson F, Downing GM, Hill J, Casorso L, Lerch N. Palliative performance scale (PPS): a new tool. J Palliat Care. 1996;12(1):5-11.
16. Oğuz G, Şenel G, Koçak N, Karaca Ş. The Turkish Validity and Reliability Study of Palliative Performance Scale. Asia Pac J Oncol Nurs. 2021;8(4):413-418. Published 2021 May 31.
17. Küçükgüçlü Ö, Esen A, Yener G. The reliability and validity of the caregiver burden ınventory in Turkey. Journal of Neurological Sciences, 2009; 26(1).
18. Ergin C. Burnout in physicians and nurses and adaptation of the Maslach Burnout Inventory. VII. National Psychology Congress, Ankara, Publications of Organization of Turkish Psychologists, 1992; pp.143-154.
19. Çam O. Examination of validity and reliability of Maslach Burnout Inventory in a sample of education nurses. J. Ege Univ. Sch. Nurs, 1996;12(3): 61-69
20. Alsirafy SA, Nagy R, Hassan AD, et al. Caregiver burden among family caregivers of incurable cancer patients in two eastern Mediterranean countries. BMC Palliat

Care. 2021; 20(1):163. Published 2021 Oct 18.

21. Ahmad Zubaidi ZS, Ariffin F, Oun CTC, Katiman D. Caregiver burden among informal caregivers in the largest specialized palliative care unit in Malaysia: a cross sectional study. BMC Palliat Care. 2020;19(1):186. Published 2020 Dec 8.
23. Saraçoğlu E, Altay B, Dönmez MV. Care Burden and Burnout Levels in Caregivers Family Members of Cancer Patients. The Journal of Academic Social Science,2022;10(124): 370-382.
24. Egici MT, Kök Can M, Toprak D, Zeren Öztürk G, Esen ES, Özen B, et al. Care Burden and Burnout Status of Caregivers Whose Patients are Treated in Palliative Care Centers. JAREN, 2019;5(2):123 - 131.
25. Cross AJ, Garip G, Sheffield D. The psychosocial impact of caregiving in dementia and quality of life: a systematic review and meta-synthesis of qualitative research. Psychol Health. 2018;33(11):1321-1342.
26. Guerriere D, Husain A, Zagorski B, et al. Predictors of caregiver burden across the home-based palliative care trajectory in Ontario, Canada. Health Soc Care Community. 2016;24(4):428-438.
27. Schwartz K, Beebe-Dimmer J, Hastert TA, et al. Caregiving burden among informal caregivers of African American cancer
22. Krug K, Miksch A, Peters-Klimm F, Engeser P, Szecsenyi J. Correlation between patient quality of life in palliative care and burden of their family caregivers: a prospective observational cohort study. BMC Palliat Care. 2016; 15:4. Published 2016 Jan 15.

survivors. J Cancer Surviv. 2021;15(4):630-640.

28. Fu W, Li J, Fang F, Zhao D, Hao W, Li S. Subjective burdens among informal caregivers of critically ill patients: a cross-sectional study in rural Shandong, China. BMC Palliat Care. 2021;20(1):167. Published 2021 Oct 22.
29. Janze A, Henriksson A. Preparing for palliative caregiving as a transition in the awareness of death: family carer experiences. Int J Palliat Nurs. 2014;20(10):494-501.
30. Gérain P, Zech E. Do informal caregivers experience more burnout? A meta-analytic study. Psychol Health Med. 2021;26(2):145-161.
31. Hiyoshi-Taniguchi K, Becker CB, Kinoshita A. What Behavioral and Psychological Symptoms of Dementia Affect Caregiver Burnout?. Clin Gerontol. 2018; 41(3):249-254.

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Surgical Treatment of Low-Grade Lumbar Spondylolisthesis

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Research Article

History

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ABSTRACT

Lumbar spondylolisthesis is a prevalent cause of lower back pain and is a focal interest of spinal surgery. A diverse set of decompression and fusion techniques are used in surgery.
To investigate the surgical and clinical outcomes patients with spondylolisthesis who received surgical intervention.
Data from 25 patients (15 women; 10 men; mean age, 48.8 ± 12.4 years; range, 27–66 years) with low-grade spondylolisthesis who received surgical intervention were retrospectively analyzed. Posterolateral and posterior interbody fusion was used in 17 and 8 patients, respectively, and 19 received posterior pedicle screws and 6 received only fusion and decompression.
According to the Kirkaldy–Willis criteria, the clinical outcomes of 11 (44%), 9 (36%), 3 (12%), and 2 (8%) patients were rated excellent, good, fair, and poor, respectively, with a success rate of 80%. Furthermore, fusion was observed in 21 patients (84%). Favorable outcomes were achieved in 17 (90%) patients with pedicle screws and in 3 (50%) with only decompression and fusion (p=0.048; p<0.05). The rate of favorable outcome was 75% of patients who smoked (p=0.226; p>0.05). Two out of three patients with revision surgery had poor clinical outcomes (p=0.091; p<0.05).
The addition of pedicle screw fixation to posterolateral fusion increases fusion rates and yields satisfactory clinical results. Previous history of surgery is a risk factor that should be considered before deciding to perform surgery. Furthermore, the transpedicular screw fixation technique can be made less complicated and effective via effective and experienced teamwork. Herein, we reviewed recent studies and discussed the indications, complications, and outcomes of surgical treatment of low-grade spondylolisthesis.

Keywords: Lumbar spondylolisthesis, pedicle screws, fusion

Düşük Dereceli Lomber Spondilolistezisin Cerrahi Tedavisi

Süreç

Geliş: 31/07/2023
Kabul: 26/09/2023

ÖZ

Lomber spondilolistezis bel ağrısının yaygın bir nedenidir ve omurga cerrahisinin odak noktasıdır. Cerrahide çok çeşitli dekompresyon ve füzyon teknikleri kullanılmaktadır.
Cerrahi girişim uygulanan spondilolistezisli hastaların cerrahi ve klinik sonuçlarını araştırmak.
Düşük dereceli spondilolistezis nedeniyle cerrahi girişim uygulanan 25 hastanın (15 kadın; 10 erkek; ortalama yaş, 48,8 ± 12,4 yıl; aralık, 27-66 yıl) verileri retrospektif olarak analiz edildi. Sırasıyla 17 ve 8 hastaya posterolateral ve posterior interbody füzyon uygulandı ve 19'una posterior pedikül vidası, 6'sına ise sadece füzyon ve dekompresyon uygulandı.
Kirkaldy-Willis kriterlerine göre 11 (%44), 9 (%36), 3 (%12) ve 2 (%8) hastanın klinik sonuçları mükemmel, iyi, orta ve kötü olarak derecelendirildi. sırasıyla %80 başarı oranıyla. Ayrıca 21 hastada (%84) füzyon gözlendi. Hastaların 17'sinde (%90) pedikül vidası, 3'ünde (%50) ise sadece dekompresyon ve füzyon ile olumlu sonuçlar elde edildi (p=0,048; p<0,05). Sigara içen hastalarda olumlu sonuç oranı %75 idi (p=0,226; p>0,05). Revizyon cerrahisi yapılan üç hastanın ikisinde kötü klinik sonuçlar elde edildi (p=0,091; p<0,05).
Posterolateral füzyona pedikül vidası fiksasyonunun eklenmesi füzyon oranlarını arttırmakta ve tatmin edici klinik sonuçlar vermektedir. Önceki ameliyat öyküsü, ameliyata karar vermeden önce dikkate alınması gereken bir risk faktörüdür. Ayrıca etkili ve deneyimli bir ekip çalışmasıyla transpediküler vida tespit tekniği daha az karmaşık ve etkili hale getirilebilir. Burada güncel çalışmaları gözden geçirdik ve düşük dereceli spondilolistezisin cerrahi tedavisinin endikasyonlarını, komplikasyonlarını ve sonuçlarını tartıştık.

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Anahtar sözcükler: Lomber spondilolistezis, pedikül vidaları, füzyon

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Introduction

Lumbar spondylolisthesis is an important cause of spinal canal stenosis and is often associated with back and leg pain, restriction in daily activities, and significant work disability. Various techniques intended for the surgical treatment of lumbar spondylolisthesis have been developed thus far, and the development of new techniques has continued. [1,2,3,4] No golden standard for the surgical treatment of spondylolisthesis has been established thus far. Fusion is an indispensable part of spondylolisthesis treatment and other conditions of spinal instability. However, achieving adequate fusion and favorable clinical outcomes is not always possible in adults with spondylolisthesis. [5] The technique involving stabilization with the posterior pedicle screw has garnered increased use in recent years and was believed to provide a better solution. The disadvantages of this technique include that it is a major surgical procedure, has relatively high complications, and is an expensive surgical technique; thus, exercising precaution during patient selection is important. [6,7] The present study aimed to determine the patient group and the extent to which the patients would benefit from surgical treatment and review the problems associated with the treatment in light of the recent studies.

Material and Method

This retrospective study included 25 patients who received surgical intervention for low-grade lumbar spondylolisthesis between September 1991 and January 1998 at the Neurosurgical Clinics of Atlas University Medicine Hospitaltal. The article was derived from a dissertation study. Study data, including age, sex, preoperative complaints, physical examination, and radiologic findings, were recorded. Patients underwent follow-up examinations and radiologic tests for a mean period of 31 months (range from 6 months to 4 years) postoperatively. Kirkaldy–Willis criteria (excellent, good, fair, and poor) were used to assess the effectiveness of the surgical intervention. [8] The patients deemed eligible for surgery showed clinical and radiological findings compatible with spondylolisthesis, and these patients did not benefit from conservative treatment methods, including bed rest, medical treatment, and physical therapy and rehabilitation. The prerequisites for surgical indication were neurologic deficit, neurogenic claudication, spondylolisthesis, and postural abnormality, among others.

Dynamic lumbosacral radiography was used to radiologically confirm spondylolisthesis, a tensional movement of ≥4 mm, in the patients. The techniques accommodated during the surgical interventions included fenestration, laminectomy, posterior lumbar interbody fusion (PLIF) with no cage, posterolateral fusion (PLF), and stabilization with posterior pedicle screw technique. A combination of these techniques was used based on the indication of the cases. Reduction was not used in any patient. Autologous graft, collected from the iliac wing bone, was used for fusion. Fusion was believed to have occurred upon observation of bilateral trabecular bone continuity between the fused segments.

Statistical Analyses

The Number Cruncher Statistical System (NCSS) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA) was used for statistical analysis. Fisher's Exact Test was used to compare qualitative data. Results were analyzed at a 95% confidence interval, and a p level of <0.05 indicated statistical significance.

Surgical Technique

Patients were placed in a prone position to expose the abdomen. Prophylactic antibiotherapy was administered, and surgery was commenced under general anesthesia after determining the vertebral level using fluoroscopy. A vertical incision was made into the midline to clearly view the surgical area. The paravertebral muscles were bilaterally, subperiosteally dissected, after which the laminae, facet joints, pars interarticularis, and transverse processes were exposed. Pedicle screw entry points at the instrumentation levels were set using the intersection technique. First, the entry point was prepared with a curette and then the screw path was prepared with a special pedicle curette, while accounting for the transverse and sagittal pedicle angles. Meanwhile, the screw path was intermittently controlled using Kirshner wires. When a transition from cortical bone to soft tissue was detected, another nearby point was selected to provide secure fixation. After determining the screws according their respective levels, the screws were placed into the prepared pathways in an orientation as appropriate to their angles. Due care was taken to avoid trespassing the anterior cortex in terms of implantation depth. Necessary decompression was then performed. Bone graft from the iliac wing bone was shaped to fit the distance in cases of interbody fusion. The graft was placed in the disc space, allowing minimal neural manipulation. The posterior lumbar fusion (PLF) was placed in the form of lamellae on the facets and between the transverse processes. Screw–rod connection was ensured by shaping the rods to fit their physiologic curvatures. Hemostasis was achieved before closure.

Results

Among the 25 patients who received surgical intervention for lumbar spondylolisthesis, 10 were male (40%), 15 were female (60%), and the mean patient age was 48.8 ± 12.4 years (range, 27–66 years). (Figure 1) Lower back pain was the leading complaint at a presentation by all the patients included in the study. (Table 1) Pain radiating to the leg was unilateral in 14 patients and bilateral in 4. The mean duration of pain experienced by the patients was 4.8 years (range, 4 months to 11 years). Upon physical examination of the patients, the most prevalent finding was the positive straight leg raising test and sensory deficit (Table 2).

Figure 1. Distribution of cases based on age and gender.

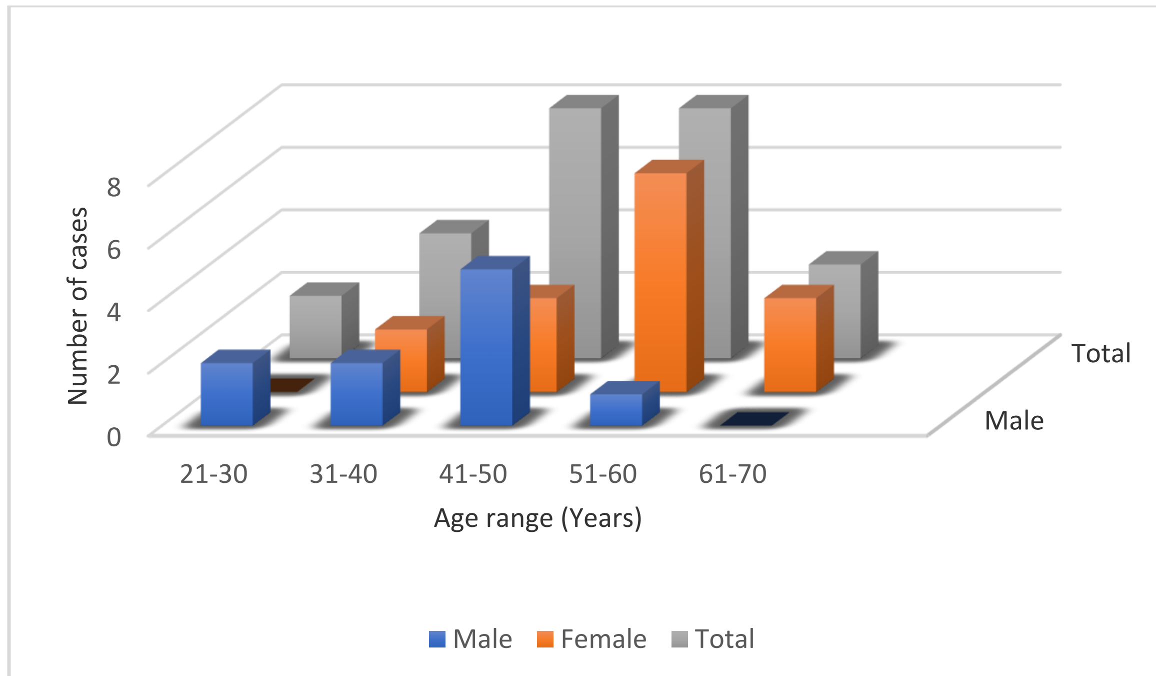


Table 1. Patients' complaints at admission

Symptoms	Number of cases (%)
Lower back pain	25 (100%)
Pain radiating to the leg	18 (72%)
Muscle weakness	5 (20%)
Numbness in the foot	4 (16%)

Table 2. Examination findings of the patients

FINDINGS	Case (%)
Straight leg raise test	18 (72%)
Motor deficit	11 (44%)
Sensory deficit	18 (72%)
Reflex deficit	12 (48%)
Neurogenic claudication	7 (28%)
Atrophy	5 (20%)

The mean slippage rate was 24% (range, 15%–51%) based on Tailard's method. [9] Furthermore, isthmic, degenerative, and postoperative spondylolisthesis was observed in 11, 13, and 1 patients, respectively (Figure 2). The age of patients with degenerative spondylolisthesis was 41–60 years, whereas patients with isthmic spondylolisthesis were distributed across all age groups (Figure 3).

Spondylolisthesis was at the level of L5–S1 in 11 patients, L4–5 in 9, L3–4 in 4, and L2–3 in 1. Comorbid lumbar stenosis and lumbar disc herniation was observed in 9 and 7 patients with spondylolisthesis, respectively. Of the 19 patients who received stabilization with the posterior pedicle screw technique, 4 had six screws, and 15 had four screws. A total of 6 patients only underwent decompression and PLF, whereas 19 patients underwent fenestration and foraminotomy, with 6 patients receiving decompression with laminectomy. PLF was performed in 17 patients, and PLIF was performed in the remaining 8 patients. The mean duration of

hospitalization was 13.5 days, and the mean duration of surgery was 3.5 hours.

In total, 20 patients were rated as excellent or good and 5 as fair or poor based on the Kirkaldy–Willis Grading system. Good outcome was observed in 17 (90%) patients with pedicle screws and in 3 (50%) patients with only decompression and fusion. The difference was significant (p=0.048; p<0.05), with a higher rate of good outcome in the patients with pedicle screws. In patients who smoked, 75% of the patients showed good results. The patients who smoked showed no significant difference when compared with those who did not smoke (p=0.226; p<0.05).

The clinical outcome in patients without revision surgery was good in 19 patients (86.4%). A good outcome was achieved in only one of the 3 patients (33.3%) who received revision surgery. Although the difference was not significant, the p value was close to the level of significance. A significantly high rate of good outcomes was noted in patients who did not undergo revision surgery (p=0.091; p<0.05). Radiologic examination revealed the absence of an increase in the slippage percentage in these patients. Furthermore, fusion was observed in 21 patients (84%).

Figure 2. Distribution of the type of spondylolisthesis

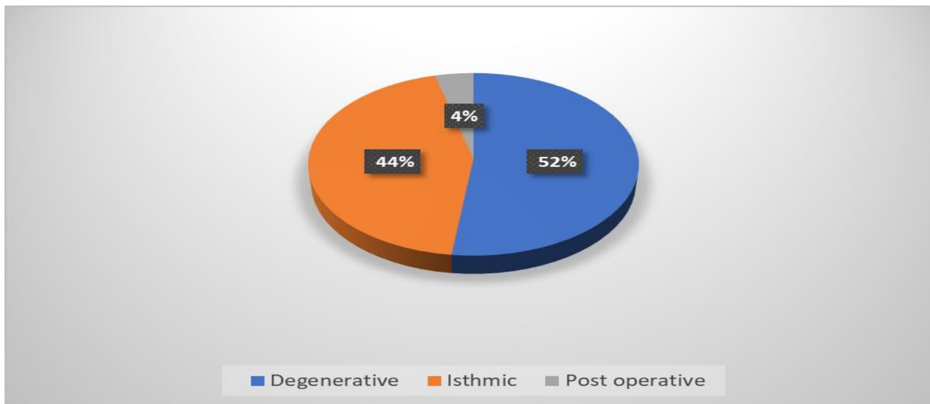
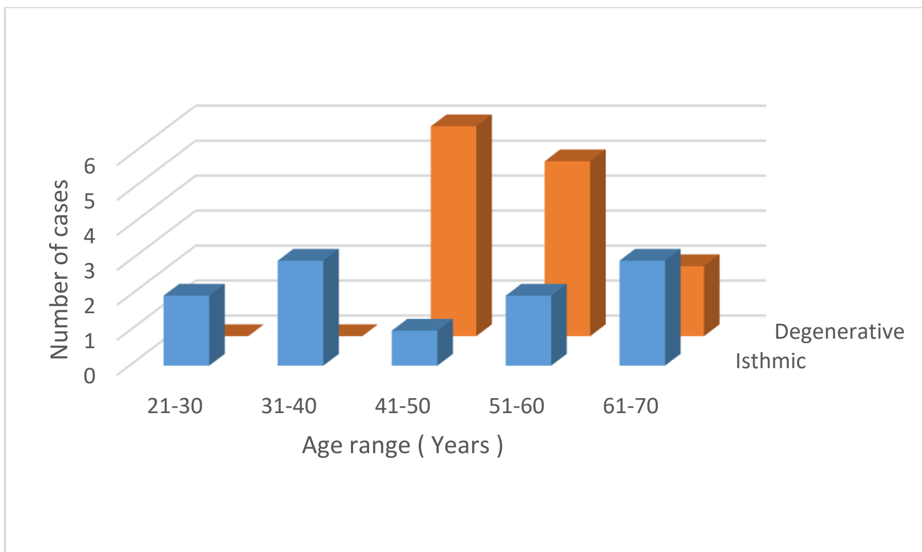


Figure 3. Age incidence of the most common types of spondylolisthesis



Complications

Two patients with a superficial infection at the surgical site were treated via antibiotherapy and dressing. No surgical intervention was considered necessary. All patients, who received grafts from the iliac bone wing, experienced severe postoperative pain at the origin of the iliac bone area. Analgesics were used to treat pain, and these pains did not persist for a prolonged period. Major postoperative complications were observed in 5 patients. One patient experienced a cerebrospinal fluid (CSF) fistula, which was successfully managed with conservative treatment involving measures such as bed rest, maintaining an upright position, and avoiding activities that could raise intracranial pressure, including lifting and straining. Wound care was administered using dressings, and by the third day, the leakage had ceased. One patient had an abscess at the paravertebral muscles, which was treated by draining the abscess and administering antibiotherapy. In one patient, root compression occurred upon narrowing the foramen because the screw appeared to be misoriented; this was treated by repositioning the screw during revision surgery. The grafts in one patient with PLIF had slipped into the spinal canal, and pedicle screw penetration was visible via the lumbar computed tomography imaging performed for control purposes. The reoperated patient had bone grafts removed from the disc space and PLF and screw repositioning were performed. The patient's clinical condition did not improve after revision surgery, and therefore, the instruments were removed through reoperation. In another patient who had undergone PLIF, the grafts had slipped into the spinal canal, inducing increased pain. The patient was treated by repositioning the grafts and removing the compression, which resulted in successful decompression.

Discussion

A golden standard for the principles of surgical treatment for low-grade spondylolisthesis has not been established thus far, and debate regarding decompression, fusion technique, instrumentation, and graft type is ongoing. Furthermore, different techniques have been used, which include microdecompression [10], transvertebral screw fixation [11], and defect repair with screws and hooks[12] and with screws and wiring [13]. Significant treatment progress could have been achieved through the introduction of spinal instrumentation in the treatment of spondylolisthesis. However, on the grounds that conventional treatment methods continue to be indispensable, fusion can only be achieved in combination with spinal instrumentation. The aim of surgical treatment in the treatment of spondylolisthesis should be to prevent deficits, provide maximum improvement in existing deficits, relieve pain, ensure stability, stop the progression of slippage, and improve quality of life [14].

Most patients with low-grade spondylolisthesis without neurologic deficit benefit from conservative treatment. [15, 16] Evan D Boyd et al. studied a group of 46 patients with grade 1 spondylolisthesis and spondylolysis and reported that favorable outcomes can be achieved through conservative treatment. [17] Nava-Bringas et al. achieved good outcomes in terms of pain and function in a study with exercise groups and reported no difference in clinical outcome between different exercise programs. [18] However, Matsunaga suggested that listhesis may increase up to 30% after conservative treatment. [19]

Although fusion is one of the main principles of treatment in spondylolisthesis, only decompression can achieve minimal intervention. A review of the clinical results in patients who underwent decompression without fusion revealed highly satisfactory results. [20, 21, 22] However, Jang JW et al. suggested that slippage increased in cases where decompression alone was performed. [23] Muslim et al. reported that bilateral microdecompression with unilateral intervention was associated with satisfactory results, and there was no increase in slippage. [24]

Reportedly, a clinically significant difference in quality of life was observed in patients with degenerative low-grade spondylolisthesis following the addition of lumbar spinal fusion to decompression. [25, 26] Takahiro Tsutsumimoto et al. achieved a 69% recovery rate after decompression and non-instrumented fusion. [27] Despite a 74% fusion in the above series, no significant difference was noted in terms of the clinical outcome between those with and without fusion. However, previous studies with fusion alone, reported a significant rate of pseudoarthrosis compared with instrumented fusion. [28] In their review article, Martin et al. reported that fusion had a favorable effect on the clinical outcome compared with the clinical outcomes of patients who underwent decompression alone. Accordingly, they reported that the use of instruments increased fusion rates but did not ensure significant superiority in terms of clinical outcome.

A study combined fusion and decompression and reported satisfactory outcomes through the use of instrumented fusion and interbody fusion at a rate of 77% and 79%, respectively, compared with 64%

satisfactory results with fusion alone. [29] Yong-ping Ye et al. suggested that instrumentation increased fusion rates but was not associated with satisfaction. [30] In the present study, all the patients received fusions with a success rate of 84%. The fusion rate was variable in adults, and obesity, osteoporosis, smoking, and systemic diseases may lead to lower-than-expected results. [31] Fusion rates were better in children than in adults. According to a study by Jalenko et al., 85% fusion was achieved in children who received non-instrumented intervention in isthmic spondylolisthesis, whereas the same rate was 65% in adults. [32]

PLIF can be performed in patients undergoing discectomy. In recent years, the application of PLIF technique has become increasingly popular. As observed in the present study, PLIF is performed with cages in the majority of cases despite the fact that PLIF was typically performed without cages in the past. However, anterior lumbar interbody fusion (ALIF) and PLIF alone were reported to be biomechanically inferior to instrumented fusion and were not considered a standard for spinal fusion. [33, 34] Therefore, PLIF may be considered suitable for use in instrumented fusion surgeries. A number of previous studies have reported successful results using PLIF. In most of those studies, a higher rate of fusion was obtained through PLIF than via PLF. [35, 36] However, the existence of a difference between the two methods in terms of clinical outcome remains unclear. In their review article, Okuda et al. reported that a mean of 82% satisfactory results were achieved in the PLIF series. [37] Liu et al. suggested that PLIF was associated with fewer complications and higher fusion rates than PLF. [38]

Instrumentation has been adopted by a wide range of authors on the grounds that it provides a rigid fixation and increases the likelihood of fusion. Fixation, when combined with decompression, reduces pain, stops deformity progression, and allows for early mobilization. The transpedicular screw system is the most preferred technique because pedicle screws provide biomechanically stronger three-column stabilization than other fixation options. Pedicle screws do not require an intact posterior element. Despite the risk of neural damage, CSF fistula, vascular damage, and increased risk of infection, pedicle screws have been proven to be safe in experienced hands.

Whether bone fusion correlates with clinical outcome remains a controversial issue. Certain authors reported that clinical outcomes correlated well with fusion rates. [39] However, Fritzell et al. suggested that radiologic fusion did not correlate significantly with clinical outcome. [40] Inamdar et al. preferred PLF to PLIF due to the simplicity of the procedure, low rate of complications, and better clinical and radiologic results, although both groups reported a fusion rate of 100%. [41] Hallett et al. compared decompression alone, PLF + pedicle screw, and transforaminal lumbar interbody fusion (TLIF) + pedicle screw technique and reported that >90% fusion was achieved in the PLF group without significant intergroup difference in terms of functional results. [42] In the cases included in the present study, the clinical outcome was good or excellent in 90% of the patients, who underwent pedicle screws.

Fischgrund et al. investigated the effect of instrumentation in lumbar stenosis secondary to degenerative spondylolisthesis in a prospective randomized study. Sixty-seven patients received instrumented and non-instrumented decompression and fusion. After completing the follow-up, fusion rates of 82% and 48% were achieved in instrumented and non-instrumented cases, respectively. [43] Considering that there were reports on patients with spondylolisthesis, who received pedicle screw fixation without any success, despite an increased fusion rate, solid fusion was believed to not be the only factor that influenced clinical outcomes. Despite a fusion rate of 84% in the cases included in the present study, the good clinical outcome rate was 80%.

Fusion assessment was reported to be challenging in several studies, and identifying fusion using radiologic examinations is particularly difficult in all cases. Pseudoarthrosis may be painful as well as asymptomatic. [44] When patients who were radiologically considered to have fusion underwent re-operation for other etiologies, some patients appeared to not have fusion. Therefore, it can be suggested that “the best identification of fusion is by intraoperative inspection, albeit not practical.” [45]

Smoking is an important risk factor associated with preventing return to pre-disease activity and pain relief. In studies with a number of fusion series, poor results and high pseudoarthrosis rate were reported among smokers. [31, 44] However, studies in the past have also suggested that smoking had no effect on fusion. [45] Although the rate of clinically good outcome was lower (75%) in smokers in the present study, this rate was not significant.

The need for revision surgery was one of the most prominent factors affecting the outcome of lumbar decompression and fusion surgery. [36] A recent study reported a 13.5% re-operation rate in a database analysis of lumbar fusion surgery. [46] Patients who underwent repeated operations showed

remarkably poor outcomes, and even in cases of re-operation, the results were unsatisfactory. [36] Seung-Pyo Suh et al. reported a fusion rate of 71% in patients, who underwent revision surgery for pseudoarthrosis, with satisfactory results in only 52%. [47] Derman et al. reported in a review article that revision with PLF resulted in pseudoarthrosis in 35%–51% of cases. In addition, no significant difference was observed between different techniques, including TLIF, ALIF, and PLIF, in terms of patients' quality of life after PLF revision surgeries. Therefore, a study suggested that the surgical strategy of each revision case should be different. [48] In the series included in the present study, 3 cases underwent revision surgery and had a good clinical outcome rate of 33%. A major infection occurred in one patient (4%), consistent with the reported rate of 0.7%–11.9%. [49] Contrary to the previous studies, the instrument did not have to be removed as a result of the infection.

Limitations

The primary limitation to the present study was the comparatively low number of cases. More optimized results could be achieved through future studies with a larger number of cases. Another limitation is that the factors that might have an effect of fusion and satisfaction rates could not be comprehensively investigated. This is attributable to the retrospective nature of the study. Therefore, future prospective studies should address the issue in a more detailed approach by accommodating different parameters.

Conclusion

Several alternatives to the surgical treatment exist intended for low-grade spondylolisthesis. The widespread use of a modern and contemporary stabilization technique, including the posterior pedicle screw in orthopedics and neurosurgery, has opened new horizons in spinal surgery. The fusion rates have increased and better stabilization can be achieved through the pedicle screw technique. It is widely accepted that the most effective stabilization can be provided using fusion. Therefore, the combination of pedicle screw fixation and fusion, with the addition of decompression, as necessary, may be considered the ideal surgical method. However, patient selection is one of the most important aspects of treatment. Previous surgery is an important risk factor that should be considered before deciding the surgical treatment. In conclusion, it is possible to make use of the transpedicular screw fixation technique in a less complicated and effective approach through an effective and experienced teamwork.

Conflict Of Interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

References

1. Santoni BG, Hynes RA, McGilvray KC, Rodriguez-Canessa G, Lyons AS, Henson MA, et al. Cortical bone trajectory for lumbar pedicle screws. Spine J. 2009;9:366-73.
2. Holly LT, Foley KT. Three-dimensional fluoroscopy-guided percutaneous thoracolumbar pedicle screw placement. Technical note. J Neurosurg. 2003;99;Suppl:324-9.
3. Lee CK, Park JY, Zhang HY. Minimally invasive transforaminal lumbar interbody fusion using a single interbody cage and a tubular retraction system: technical tips, and perioperative, radiologic and clinical outcomes. J Korean Neurosurg Soc. 2010;48:219-24.
4. Grob D, Humke T, Dvorak J. Direct pediculo-body fixation in cases of spondylolisthesis with advanced intervertebral disc degeneration. Eur Spine J. 1996;5:281-5.
5. Wang SJ, Han YC, Liu XM, Ma B, Zhao WD, Wu DS, et al. Fusion techniques for adult isthmic spondylolisthesis: a systematic review. Arch Orthop Trauma Surg. 2014;134:777-84.
6. Aimar E, Iess G, Mezza F, Gaetani P, Messina AL, Todesca A, et al. Complications of degenerative lumbar spondylolisthesis and stenosis surgery in patients over 80 s: comparative study with over 60 s and 70 s. Experience with 678 cases. Acta Neurochir (Wien). 2022;164:923-31.
7. Fehlings MG, Rabin D. Surgical complications in adult spondylolisthesis. J Neurosurg Spine. 2010;13:587-8; discussion 588.
8. Kirkaldy-Willis WH, Paine KW, Cauchoix J, McIvor G. Lumbar spinal stenosis. *Clin Orthop Relat Res*. 1974;(99):30-50.
9. Taillard WF. Etiology of spondylolisthesis. *Clin Orthop Relat Res*. 1976;(117):30-39.
10. Austevoll IM, Gjestad R, Solberg T, Storheim K, Brox JI, Hermansen E, et al. Comparative effectiveness of microdecompression Alone vs decompression plus instrumented fusion in lumbar degenerative spondylolisthesis. JAMA Netw Open. 2020;3:e2015015.
11. Chen SR, Gibbs CM, Zheng A, Dalton JF, Gannon EJ, Shaw JD, et al. Use of L5-S1 transdiscal screws in the treatment of isthmic spondylolisthesis: a technical note. J Spine Surg. 2021;7:510-5..

12. Zayan M, Hussien MA, El Zahlawy H. Pars interarticularis repair using pedicle screws and laminar hooks fixation technique in patients with symptomatic lumbar spondylolysis. SICOT J. 2022;8:13.
13. Pai VS, Hodgson B, Pai V. Repair of spondylolytic defect with a cable screw reconstruction. Int Orthop. 2008;32:121-5.
14. Tang L, Wu Y, Jing D, Xu Y, Wang C, Pan J. A Bayesian network meta-analysis of 5 different fusion surgical procedures for the treatment of lumbar spondylolisthesis. Med (Baltim). 2020;99:e19639.
15. Bydon M, Alvi MA, Goyal A. Degenerative lumbar spondylolisthesis: definition, natural history, conservative management, and surgical treatment. Neurosurg Clin N Am. 2019;30:299-304.
16. Dunn AS, Baylis S, Ryan D. Chiropractic management of mechanical low back pain secondary to multiple-level lumbar spondylolysis with spondylolisthesis in a United States Marine Corps veteran: a case report. J Chiropr Med. 2009;8:125-30.
17. Boyd ED, Mundluru SN, Feldman DS. Outcome of conservative management in the treatment of symptomatic spondylolysis and Grade I spondylolisthesis. Bull Hosp Jt Dis (2013) 2019;77:172-82.
18. Nava-Bringas TI, Romero-Fierro LO, Trani-Chagoya YP, Macías-Hernández SI, García-Guerrero E, Hernández-López M, et al. Stabilization exercises versus flexion exercises in degenerative spondylolisthesis: A randomized controlled trial. Phys Ther. 2021;101:pzab108.
19. Matsunaga S, Sakou T, Morizono Y, Masuda A, Demirtas AM. Natural history of degenerative spondylolisthesis. Pathogenesis and natural course of the slippage. Spine (Phila Pa 1976). 1990;15:1204-10.
20. Eismont FJ, Norton RP, Hirsch BP. Surgical management of lumbar degenerative spondylolisthesis. J Am Acad Orthop Surg. 2014;22:203-13.
21. Mori G, Mikami Y, Arai Y, Ikeda T, Nagae M, Tonomura H, et al. Outcomes in cases of lumbar degenerative spondylolisthesis more than 5 years after treatment with minimally invasive decompression: examination of pre- and postoperative slippage, intervertebral disc changes, and clinical results. J Neurosurg Spine. 2016;24:367-74.
22. Kimura R, Yoshimoto M, Miyakoshi N, Hongo M, Kasukawa Y, Kobayashi T, et al. Comparison of posterior lumbar interbody fusion and microendoscopic muscle-preserving interlaminar decompression for degenerative lumbar spondylolisthesis with >5-year follow-up. Clin Spine Surg. 2019;32:E380-5.
23. Jang JW, Park JH, Hyun SJ, Rhim SC. Clinical outcomes and radiologic changes after microsurgical bilateral decompression by a unilateral approach in patients with lumbar spinal stenosis and Grade I degenerative spondylolisthesis with a minimum 3-year follow-up. Clin Spine Surg. 2016;29:268-71.
24. Müslüman AM, Cansever T, Yılmaz A, Çavuşoğlu H, Yüce İ, Aydın Y. Midterm outcome after a microsurgical unilateral approach for bilateral decompression of lumbar degenerative spondylolisthesis. J Neurosurg Spine. 2012;16:68-76.
25. Pazarlis K, Frost A, Försth P. Lumbar spinal stenosis with degenerative spondylolisthesis treated with decompression Alone. A cohort of 346 patients at a large spine unit. Clinical outcome, complications and subsequent surgery. Spine (Phila Pa 1976). 2022;47:470-5.
26. Ghogawala Z, Dziura J, Butler WE, Dai F, Terrin N, Magge SN, et al. Laminectomy plus Fusion versus laminectomy Alone for Lumbar spondylolisthesis. N Engl J Med. 2016;374:1424-34.
27. Tsutsumimoto T, Shimogata M, Yoshimura Y, Misawa H. Union versus nonunion after posterolateral lumbar fusion: a comparison of long-term surgical outcomes in patients with degenerative lumbar spondylolisthesis. Eur Spine J. 2008;17:1107-12.
28. Martin CR, Gruszczynski AT, Braunsfurth HA, Fallatah SM, O'Neil J, Wai EK. The surgical management of degenerative lumbar spondylolisthesis: a systematic review. Spine (Phila Pa 1976). 2007;32:1791-8.
29. Endler P, Ekman P, Möller H, Gerdhem P. Outcomes of posterolateral fusion with and without instrumentation and of interbody fusion for isthmic spondylolisthesis: A prospective study. J Bone Joint Surg Am. 2017;99:743-52.
30. Ye YP, Chen D, Xu H. The comparison of instrumented and non-instrumented fusion in the treatment of lumbar spondylolisthesis: a meta-analysis. Eur Spine J. 2014;23:1918-26..
31. Cruz A, Ropper AE, Xu DS, Bohl M, Reece EM, Winocour SJ, et al. Failure in lumbar spinal fusion and current management modalities. Semin Plast Surg. 2021;35:54-62.
32. Jalanko T, Helenius I, Remes V, Lamberg T, Tervahartiala P, Yrjönen T, et al. Operative treatment of isthmic spondylolisthesis in children: a long-term, retrospective comparative study with matched cohorts. Eur Spine J. 2011;20:766-75.
33. Voor MJ, Mehta S, Wang M, Zhang YM, Mahan J, Johnson JR. Biomechanical evaluation of

posterior and anterior lumbar interbody fusion techniques. J Spinal Disord. 1998;11:328-34.
34. DiPaola CP, Molinari RW. Posterior lumbar interbody fusion. J Am Acad Orthop Surg. 2008;16:130-9.
35. Guppy KH, Royse KE, Norheim EP, Harris JE, Brara HS. PLF versus PLIF and the fate of L5-S1: analysis of operative nonunion rates among 3065 patients with lumbar fusions from a regional spine registry. Spine (Phila Pa 1976). 2021;46:E584-93.
36. Okuda S, Fujimori T, Oda T, Maeno T, Yamashita T, Matsumoto T, et al. Factors associated with patient satisfaction for PLIF: patient satisfaction analysis. Spine Surg Relat Res. 2017;1:20-6.
37. Liu X, Wang Y, Qiu G, Weng X, Yu B. A systematic review with meta-analysis of posterior interbody fusion versus posterolateral fusion in lumbar spondylolisthesis. Eur Spine J. 2014;23:43-56.
38. Kim KT, Lee SH, Lee YH, Bae SC, Suk KS. Clinical outcomes of 3 fusion methods through the posterior approach in the lumbar spine. Spine (Phila Pa 1976). 2006;31:1351-7; discussion 1358.
39. Fritzell P, Hägg O, Wessberg P, Nordwall A, Swedish Lumbar Spine Study Group. Chronic low back pain and fusion: a comparison of three surgical techniques: a prospective multicenter randomized study from the Swedish lumbar spine study group. Spine (Phila Pa 1976). 2002;27:1131-41.
40. Inamdar DN, Alagappan M, Shyam L, Devadoss S, Devadoss A. Posterior lumbar interbody fusion versus intertransverse fusion in the treatment of lumbar spondylolisthesis. J Orthop Surg (Hong Kong). 2006;14:21-6.
41. Hallett A, Huntley JS, Gibson JN. Foraminal stenosis and single-level degenerative disc disease: a randomized controlled trial comparing decompression with decompression and instrumented fusion. Spine (Phila Pa 1976). 2007;32:1375-80.
42. Fischgrund JS, Mackay M, Herkowitz HN, Brower R, Montgomery DM, Kurz LT. 1997 Volvo Award winner in clinical studies. Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective, randomized study comparing decompressive laminectomy and arthrodesis with and without spinal instrumentation. Spine (Phila Pa 1976). 1997;22:2807-12.
43. Gruskay JA, Webb ML, Grauer JN. Methods of evaluating lumbar and cervical fusion. Spine J. 2014;14:531-9.
44. Li Y, Zheng LM, Zhang ZW, He CJ. The effect of smoking on the fusion rate of spinal fusion surgery: A systematic review and meta-analysis. World Neurosurg. 2021;154:e222-35.
45. Luszczyk M, Smith JS, Fischgrund JS, Ludwig SC, Sasso RC, Shaffrey CI, et al. Does smoking have an impact on fusion rate in single-level anterior cervical discectomy and fusion with allograft and rigid plate fixation? Clinical article. J Neurosurg Spine. 2013;19:527-31.
46. Cummins D, Hindoyan K, Wu HH, Theologis AA, Callahan M, Tay B, et al. Reoperation and mortality rates following elective 1 to 2 level lumbar fusion: A large state database analysis. Glob Spine J. 2022;12:1708-14.
47. Suh SP, Jo YH, Jeong HW, Choi WR, Kang CN. Outcomes of revision surgery following instrumented posterolateral fusion in degenerative lumbar spinal stenosis: A comparative analysis between pseudarthrosis and adjacent segment disease. Asian Spine J. 2017;11:463-71.
48. Derman PB, Singh K. Surgical strategies for the treatment of lumbar pseudarthrosis in degenerative spine surgery: A literature review and case study. HSS J. 2020;16:183-7.
49. Schimmel JJ, Horsting PP, de Kleuver M, Wonders G, van Limbeek J. Risk factors for deep surgical site infections after spinal fusion. Eur Spine J. 2010;19:1711-9.

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A Comparison of the duration of knee survival in patients with primary knee osteoarthritis who have treated viscosupplementation or arthroscopic debridement.

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Research Article

History

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ABSTRACT

To determine whether intraarticular viscosupplementation and arthroscopic debridement can delay knee arthroplasty.

142 patients who had VAS and OX-12 records from the first visit and regular control visit and who belonged to the control group who were referred to our clinic with pain and limitation of movement in the knee diagnosed with primary osteoarthritis of the knee Grade 2-3 according to the Kellgren-Lawrence Classification (KLC) and were followed up for at least 5 years (6,7 ±1,4 years) were included in the study. Of the 142 patients, 87 (61,3 %) were female and 55 (38,3%) were male. The average age of the patients was 53,2 ± 14,3. The groups were compared for average age on first admission, gender, the existance of morbid obesity and diabetes, average Visual Pain Score (VPS), and Oxford-12 Questionary (OX-12) scores, and smoking. Time between the first admission and arthroplasty was also compared.

Arthroplasty was performed in 87 (61,3%) of the 142 patients in 6,7±1,4. In the control group, which consisted of patients taking only NSAIDs, patients who were given viscosupplementation and patients who underwent arthroscopic debridement, the rate of total knee arthroplasty was 61,5%, 60,4%, and 61,9%, respectively.

We determined that despite an improvement in clinical symptoms like pain between the sixth month and the second year, viscosupplementation and arthroscopic debridement do not ameliorate the degenerative process and radiologic deterioration and do not affect on the duration until total knee arthroplasty.

Keywords: Knee osteoarthritis, treatment, viscosupplementation, arthroscopic knee debridement, microfracture, drilling

Viskosuplemantasyon veya Artroskopik Debridman Tedavisi Gören Primer Diz Osteoartritli Hastalarda Dizin Hayatta Kalma Süresinin Karşılaştırılması

Süreç

Geliş: 13/04/2023
Kabul: 15/09/2023

ÖZ

Eklem içi viskosuplementasyon ve artroskopik debridmanın diz artroplastisini geciktirip geciktiremeyeceğini belirlemek.

Kliniğimize dizde ağrı ve hareket kısıtlılığı nedeniyle başvuran ve primer osteoartrit tanısı alan, ilk muayene ve düzenli kontrolden itibaren VAS ve OX-12 kayıtları bulunan ve kontrol grubunda yer alan 142 hasta. Kellgren-Lawrence Sınıflamasına (KLC) göre Grade 2-3 olan ve en az 5 yıldır (6,7±1,4 yıl) takip edilen diz hastaları çalışmaya dahil edildi. 142 hastanın 87'si (%61,3) kadın, 55'i (%38,3) erkekti. Hastaların yaş ortalaması 53,2±14,3 idi. Gruplar ortalama ilk başvuru yaşı, cinsiyet, morbid obezite ve diyabet varlığı, ortalama Görsel Ağrı Skoru (VPS), Oxford-12 Anketi (OX-12) skorları ve sigara kullanımı açısından karşılaştırıldı. İlk başvuru ile artroplasti arasındaki süre de karşılaştırıldı.

142 hastanın 87'sine (%61,3) 6,7±1,4 artroplasti uygulandı. Yalnızca NSAİİ alan hastalar, viskosuplementasyon verilen hastalar ve artroskopik debridman uygulanan hastalardan oluşan kontrol grubunda total diz artroplastisi oranı sırasıyla %61,5, %60,4 ve %61,9 idi.

Altıncı ay ile ikinci yıl arasında ağrı gibi klinik semptomlarda iyileşme olmasına rağmen, viskosuplementasyon ve artroskopik debridmanın dejeneratif süreci ve radyolojik bozulmayı iyileştirmediğini ve total diz artroplastisine kadar geçen süreyi etkilemediğini belirledik.

Anahtar sözcükler: Diz osteoartriti, ted, viskosuplementasyon, artroskopik diz debridmanı. mikro kırılma, sondaj

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Introduction

Degenerative arthritis most frequently affects the knee, along with the hip and spine. Gonarthrosis is the progressive degenerative arthritis of the knee that causes pain and limitation of joint movement, degeneration in the joint space, and alignment disorders and is mostly varus. The incidence of knee osteoarthritis after the sixth decade of life is reported to be more than 75% [1]. Although total knee arthroplasty is accepted as the gold standard treatment for end-stage osteoarthritis, an increased incidence of complications is reported especially with advanced age and comorbidity. Conservative treatments, invasive procedures, or minor surgical interventions are necessary to avoid or delay surgery in younger ages or earlier stages, alleviate the symptoms and for patients who do not want to undergo surgery [2].

Conservative treatment options in degenerative arthritis of the knee are nonsteroid anti-inflammatory drugs (NSAID) [3], corticosteroids, physiotherapy modalities, and intraarticular viscosupplementation [4,5], while arthroscopic debridement, high tibial osteotomy, and unicompartmental or total knee arthroplasty are surgical treatment options [6,7].

As in most diseases, conservative modalities usually precede surgery. There are numerous studies evaluating the efficacy of nonsteroid NSAIDs in the literature [8]. Similarly, there are a number of studies concerning the efficacy of viscosupplementation, which has been an option for a few decades, and its comparison to NSAIDs [9,10,5]. In recent years, high density human hyaluronic acid equivalents and their combinations with Chondroitin-S are reported to increase treatment efficacy and positive results have been obtained in 60-80% of the cases [5].

In patients with knee osteoarthritis, the period between the onset of the degenerative process and total knee arthroplasty, which is a period where the patients' cartilaginous tissue is sufficient, can be termed as the survival of the knee. There are a number of studies reporting extended knee survival periods as a result of arthroscopic debridement where intraarticular cartilage pieces and meniscal debris are extracted and the concentration of destructive enzymes causing intraarticular carthilage destruction decreased. Also damaged regions are freshened via chondroplasty and microfracture techniques [11]. However, to the best of our knowledge, no study evaluates the effect of NSAIDs, viscosupplementation, and arthroscopic debridement on the period before total knee arthroplasty is deemed necessary.

Therefore, the primary end-point of this study was to investigate whether arthroscopic debridement and intraarticular viscosupplementation are effective in the treatment of degenerative arthritis of the knee and if not, whether they can delay knee arthroplasty.

Patients and Method

This study (Project no: KA20/220) was approved by Clinical Research Institutional Review Board (Approval number: 94603339-604.01.02/17473) and informed consent forms were taken from all patients. This retrospective cohort study is based on hospital records.

One hundred and ninety patients who visited our clinic with pain and limitation of movement in the knee between October 29th, 2009 and December 31st, 2015, diagnosed with primary osteoarthritis of the knee Grade 2-3 according to the Kellgren-Lawrence Classification (KLC) and were followed up for at least 5 years (6,7 ±1,4 years) were included in the study. Exclusion criteria were secondary osteoarthritis due to traumatic intraarticular fracture or dislocation, septic arthritis, cartilage destruction caused by metabolic, congenital or rheumatic causes, meniscectomy, and patients who were Grade 1 (no narrowing of the joint space or cartilage degeneration) according to the KLC classification and were given palliative treatment in addition to the patients who had Grade 4 degenerative arthritis and subsequently underwent TKA. After excluding 38 patients who did not show up for their last control visit, 142 patients including the control group were included in data analysis. All patients included in the study had normal physiologic alignments in the lower extremities.

The primary hypothesis (H_0) of the study was "Intraarticular viscosupplementation using only hyaline-20 and arthroscopic joint cartilage debridement prolongs the duration until knee arthroplasty". The control group consisted of patients who did not receive any invasive interventions and were given only combined nonsteroid anti-inflammatory drugs.

Every patient referring to the orthopedics and traumatology clinic of our hospital with complaints of pain and limitation of movement in the knee is routinely questioned for the duration of the pain and (visual analog scale) VAS scores at the onset and

first admission. The standard orthopedic examination evaluates the range of motion and flexion contractures, varus or valgus angles if present. Additionally, the Oxford Functional Score (OX-12), which has been validated and gained widespread use for measuring functional capacity, is applied to all patients**.** Predisposing factors for primary knee osteoarthritis such as age, sex, morbid obesity, diabetes, and smoking are also questioned at the first visit. The patients enrolled in this study were asked to visit at the 3rd and 6th months and once every 6 months after that. In the follow-up visits physical examination was carried out, Rosenberg standing x-rays were taken, VAS and OX-12 scores were calculated and recorded.

Of the 142 patients, 87 (61.3 %) were female and 55 (38.7%) were male. The average age of the patients was 53.2 ± 14.3 (55 – 74). The patients were followed up for a minimum 5 and maximum of 8 years (6,7±1,4 years) (Table 1)

The patients were divided into three groups; Group-1. Patients who underwent arthroscopic joint cartilage debridement and microfracture (n:42; 29,6%); Group-2. Patients who were given intraarticular viscosupplementation once a month, at least three times (n:48; 33,8); Group-3. Patients who were given only NSAIDs (n:52; 36,6%)

Table-1. Distribution of the mean age, sex, obesity, diabetes, smoking, mean VAS and OX-12 scores of the patients at the first visit.

	Control	Viscosupplementation	Arthroscopic debridement	Total	F	p
Number of patients	52	48	42	142		
Age	52,4 ± 15,3	51,4 ± 16,3	55,6 ± 14,8	53,2 ± 14,3	0,885	0,415
Female/Male	33/19 (1,48)	29/19 (1,53)	25/17 (1,47)	87/55 (1,58)	0,174	0,980
Obesity+/-	34/18 (1,89)	31/17 (1,82)	27/15 (1,80)	92/50 (1,84)	0,014	0,987
Diabetes+/-	29/23 (1,26)	27/21(1,29)	23/19 (1,21)	79/63 (1,25)	0,021	0,990
Smoking+/-	23/29 (0,79)	22/26 (0,85)	19/23 (0,83)	64/78 (0,82)	0,027	0,990
Mean VAS scores at first visit	5,0 ± 2,5	5,5 ± 2,4	5,1 ± 2,0	5,3 ± 2,2	0,619	0,540
Mean OX-12 scores at first visit	22,4 ± 5,7	24,5 ± 5,9	23,7 ± 5,7	23,5 ± 5,8	1,658	0,194

Viscosupplementation

The indication for viscosupplementation was the existence of pain restricting daily activities, the existence of KLC grade 2-3 degeneration in the patellofemoral, and femorotibial joint restricting movement, and the existance of changes which did not cause instability of intraarticular structures in magnetic resonance imaging. 20,000 Daltons Hyaline-L was injected intraarticularly following sterile draping. Viscosupplementation was applied for a minimum 3 and maximum 4 times every 6 months (Figure-1).

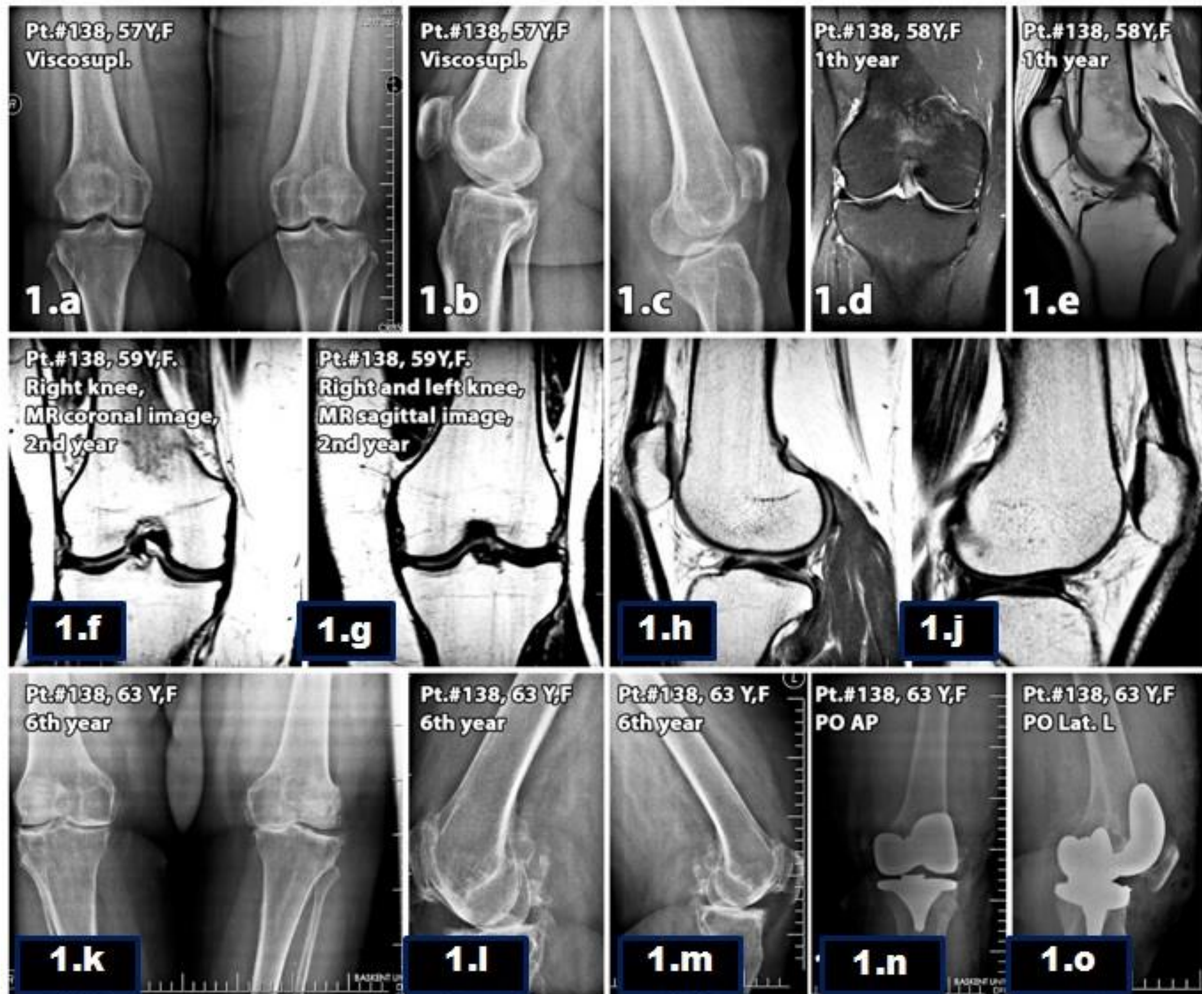

Figure-1. Pt.#138, This 57 years-old woman had Kellgren-Lawrence Classification (KLC) grade-2 degeneration at first admission. (a) AP x-ray of the knee prior to viscosupplementation three times every 6 months with Hyalen-L, (b-c) lateral x-rays of both knees, (d-j) Coronal and sagittal MR scans of both knees at 1st and 2nd years, (k-m) standing AP and lateral x-rays of both knees, (n-o) AP and lateral x-rays following total knee arthroplasty at 6th years.

Articular cartilage debridement

The indication for arthroscopic joint cartilage debridement was defined as the existence of pain that restricts daily activities, existance of knee instability with KLC grade 2-3 degeneration, osteochondral defects in the patellofemoral and femorotibial joints and existence of degenerative tears in intraarticular structures, especially in the menisci, as reported in magnetic resonance imaging.

The patients were positioned supinely under spinal anesthesia and a tourniquet was applied to the proximal femur. The joint was accessed via two standard portals and was evaluated arthroscopically. During the procedure, synovial tissues, meniscal residues, and free osteophyte bodies were removed and osteochondral lesions were shaved using a shaver and reformed using radiofrequency. Osteochondral lesions were restored using the microfracture technique. This technique was applied if an osteochondral lesion was bigger than 2 cm and cartilage surface was entirely shed. The procedure was ended after the release of the tourniquet. The patients were told not to bear weight on the operated leg for 6 months if the microfracture technique was employed (Figure-2 and 3).

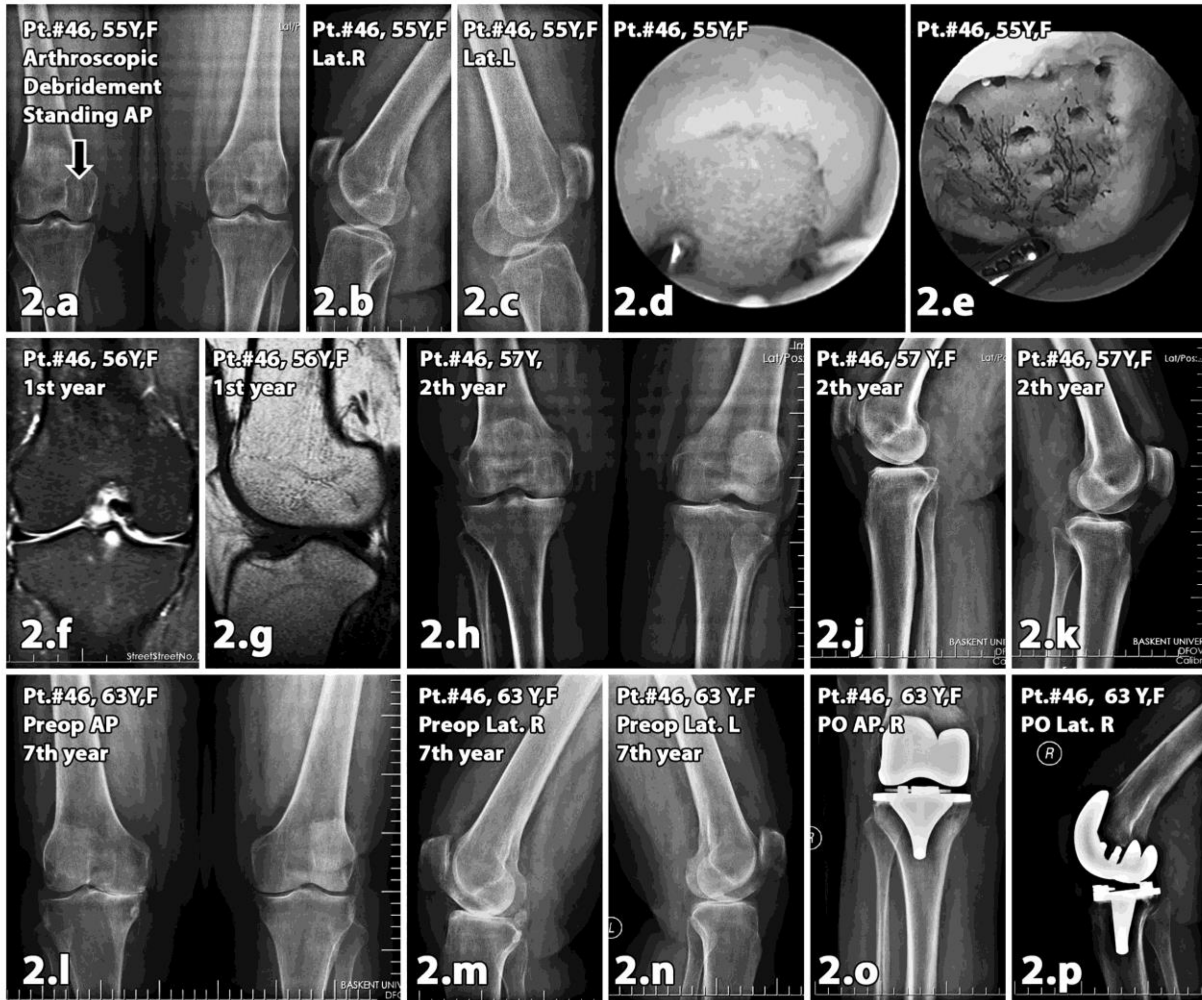

Figure-2. Pt.#46, This 55 years-old woman had Kellgren-Lawrence Classification (KLC) grade-2 degeneration at first admission. **(a)** Arrow is pointing the cartilage defect on the femoral condyl in preoperative Rosenberg AP x-rays of both knees prior to arthroscopic debridement, **(b,c)** lateral x-rays of both knees, **(d)** recordings image during arthroscopy after arthroscopic debridement of the cartilage defect, **(e)** the image after arthroskopic micro-fracture technique, **(f-h)** Coronal and sagittal MR scans of the right knee at 1st year**, (j-l)** Standing AP and lateral x-rays of both knees at 3rd year, (m,n) Standing AP and lateral X-rays of both knees at 7th year, **(o,p)** AP and lateral x-rays following total knee arthroplasty at 7th year.

Study Design

The primary endpoint of this study was to investigate whether arthroscopic debridement and intraarticular viscosupplementation are effective in the treatment of degenerative arthritis of the knee and if not, whether they can delay knee arthroplasty.

The patients were divided into three groups;
Group-1. Patients with Arthroscopic debridement and microfractures (n:42; 29,6%),

Group-2. Patients with Intraarticular Viscosupplementation administered monthly for 4 months (n:48; 33,8)
Group-3. Patients with only NSAIDs administered (Control group) (n:52; 36,6%)

The primary endpoint of this study was to investigate whether arthroscopic debridement and intraarticular viscosupplementation are effective in the treatment of degenerative arthritis of the knee and if not, whether they can delay knee arthroplasty.

In both 3 groups of 142 patients, predisposing factors for Osteoarthritis in first examination was compared. No statistically difference were found in VAS and OX-12 scores for male/female ratio, obesity, diabetes, smoking habits and KLC classification (p>0,05) (Table-1). The intergroup distribution of data when epidemiological, predisposing factors and VAS and OX-12 scores of all patients were considered was similar to the intergroup distribution (p>0,05) (Table-1).

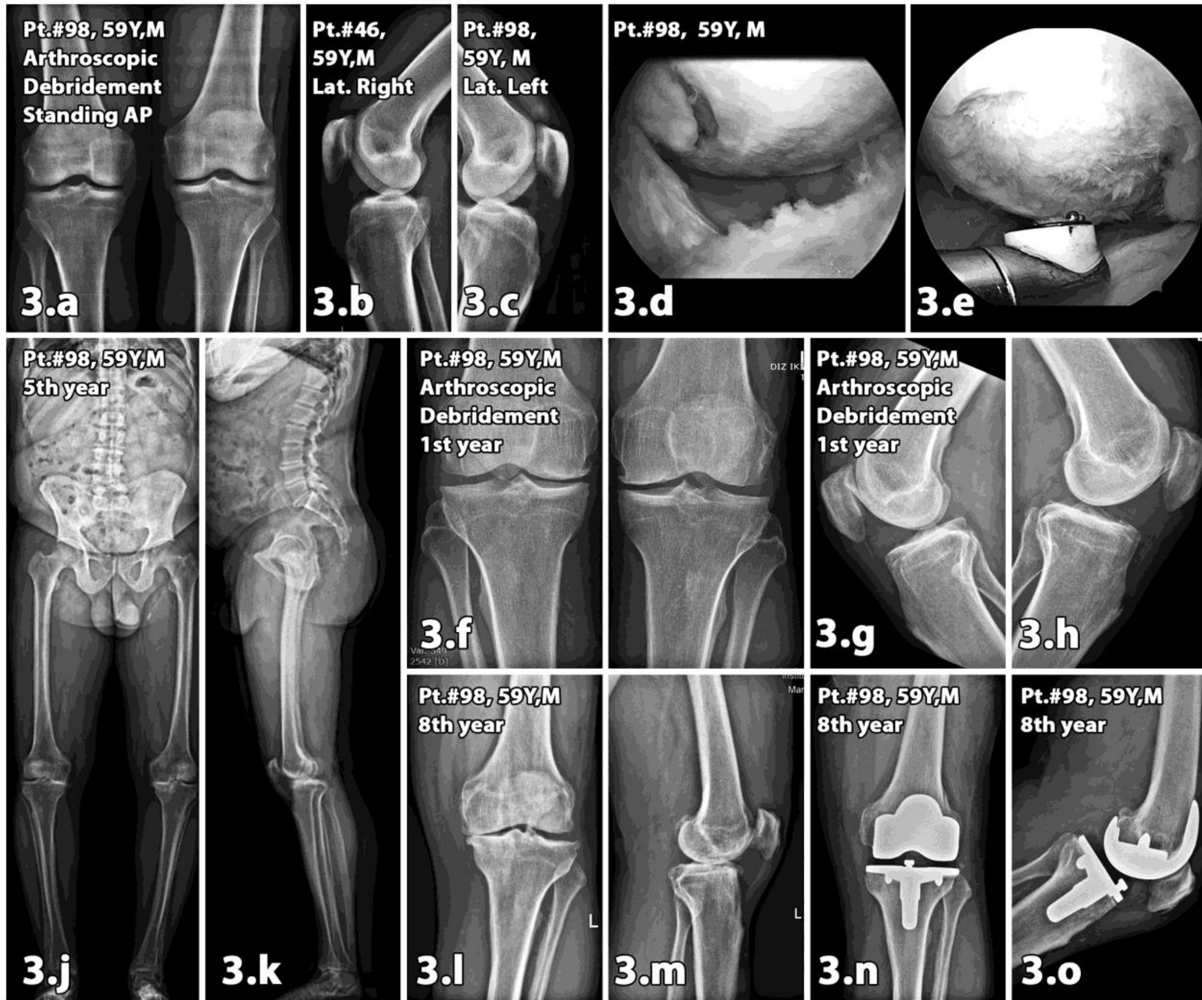

Figure-3. Pt.#98, This 59 years-old man had Kellgren-Lawrence Classification (KLC) grade-2 degeneration at first admission. **(a)** Standing Rosenberg AP x-rays of both knees prior to arthroscopic debridement, **(b,c)** lateral x-rays of both knees **(d)** image of cartilage degeneration on medial femoral condyl recording during arthroscopy, **(e)** debridement of degenerative cartilage with the radio-frequency during arthroscopy, **(f-h)** Standing AP and lateral x-rays of both knees at 1st year, **(j,k)** AP and lateral views of both knees at EOS graphies at 3rd year, **(l,m)** Standing AP and lateral x-rays of the left knee at 8th year, **(n,o)** AP and lateral x-rays following total knee arthroplasty at 8th year.

There was no statistically significant difference concerning the distribution of patients with Grade 2 and 3 degeneration based on the KLC used for radiological evaluation among groups (Table-2)

The control group consisted of patients who did not undergo any procedures until the last control. The VAS and OX-12 scores of viscosupplementation and arthroscopic debridement groıups were recorded starting at 6 months after the procedure, once a year.

The last controls were performed between October 1st, 2022- January 1st, 2023. At the last control, radiological results in addition to the history of total knee arthroplasty, if carried out, and the period between the first and the last visit was recorded.

For the patients who underwent knee arthroplasty, the VAS and OX-12 scores before the operation were recorded while for those who did not undergo surgery, the VAS and OX-12 scores at the last visit were recorded.

In this study; 87 (61,3%) of the 142 patients underwent knee arthroplasty. The distribution of these 87 patients among groups were statistically evaluated. Number of patients who did not undergo knee arthroplasty (knee survival) at the last control and their distribution among groups. The time between the first visit and the knee arthroplasty. The groups were statistically compared for the average time between these two-time points. The average VAS and OX-12 scores of the patients at the first visit, at biannual control visits, and the last

control were determined. For the patients who had undergone knee arthroplasty before the last control, the OX-12 and VAS scores before the operation were used.

Variables tested:

1- Of 142 patients in this study, 87 (% 61.3) patients underwent knee arthroplasty and statistically evaluated (Table-3).

2- Duration between first examination and if applied, time of knee arthroplasty application and statistical analysis (Table-4).

3- All groups statistical comparison in terms of OX-12 and VAS scores at 6th month follow ups.

Statistical Analysis

The SPSS 25.0 program was used in the statistical analyses, variance analysis test (F), Pearson Correlation Test (r), Ki-Square Test (X^2) were also used. The value of probability was set as p: 0.05.

Table.2. Distrubation of the patients according to the Kellgren-Lawrence Classification (KLC) at the first visit.

	KLC Grade-2	KLC Grade-3	Total (%)
Control	22/52 (0,423)	30/52 (0,577)	52 (36,7 %)
Viscosupplementation	20/48 (0,417)	28/48 (0,588)	48 (33,8 %)
Arthroscopic debridement	18/42 (0,429)	24/42 (0,541)	42 (29,5 %)
Total	59/142 (0,416)	83/142 (0,585)	142 (100 %)
X^2	0.028		
p	0.986		

Table-3. Distrubation of the number and rate of the patients with or without TKA according to treatment groups at the last control visit.

	Number and ratio of the patients who underwent TKA	Number and ration of the patients who did not undergo TKA	X^2	*p*
Control 52 (36,7 %)	**32 / 52 (61,5 %)**	**20 / 52 (38,5 %)**	**0.017**	**0.991**
Viscosupplementation48 (33,8 %)	**29 / 48 (60,4 %)**	**19 / 48 (39,6 %)**		
Arthroscopic debridement 42 (29,5 %)	**26 / 42 (61,9 %)**	**16 / 42 (38,1 %)**		
Total 142 (100 %)	**87 / 142 (61,3 %)**	**55 / 142 (38,7 %)**		

Table-4. Distrubation of the number and rate of the patients who were opereted with TKA and mean time untill TKA operation since first admitance (years) according to treatment groups.

	Number and ratio of patients who underwent TKA	Average time until TKA (years)
Control 52 (36,7 %)	32 / 52 (61,5 %)	5,9 ± 1,9
Viscosupplementation48 (33,8 %)	29 / 48 (60,4 %)	6,4 ± 2,4
Arthroscopic debridement 42 (29,5 %)	26 / 42 (61,9 %)	6,0 ± 2,1
Total 142 (100 %)	87 / 142 (61,3 %)	6,1 ± 2,2
F	0.017	0.745
p	0.991	0.476

Results

Variables such as average age, male/female ratio, morbid obesity, smoking, existance of diabetes, and VAS scores at the first visit were compared and no statistically significant difference was found (p>0,05) (Table-1).

This result shows that groups were statistically similar at the first visit for comorbidities and demographic variables such as age and sex. To better assess the effectiveness of viscosupplementation and arthroscopic debridement, we aimed to investigate obesity and diabetes across groups, which are reported as factors that speed up the degenerative process in the literature and did not find a significant difference concerning these two diseases (p>0,05) (Table-1). There was no statistically significant difference between groups concerning the ratio of KLC grade 2/grade 3 patients when the degeneration and loss of joint space based on K-L classification was evaluated (p>0,05) (Table -2).

An average of 6,7±1,4 years (5-8 years) of retrospective records were evaluated. 87 (61,3%) of the patients had undergone total knee. The rate of operation due to total knee arthroplasty indication in the control group which consisted of patients who were given NSAID only, viscosupplementation groups, and the arthroscopic debridement group was 61,5%, 60,4% and 61,9% respectively. There was no difference between these groups concerning the ratio of patients who underwent total knee arthroplasty (p>0,05) (Table-3).

The patients who underwent total knee arthroplasty and were Grade 2 and 3 at the first visit had radiological findings of increased degeneration and had become Grade 4 at the last control. Their VAS scores were greater than 8 and the OX-12 scores were above 40. The indication for knee arthroplasty was determined based on the study by Dawson et al[15], published in 1998. There was no statistically significant difference concerning the period between the first visit and knee arthroplasty (p>0,05) (Table-4).

Despite the lack of a statistically significant difference, the control group had a relatively shorter time until TKA. As a result, viscosupplementation and arthroscopic debridement did not affect on degenerative process and did not prolong the time until knee arthroplasty. Thus the H^0 hypothesis was refuted.

There was no statistically significant difference between viscosupplementation and arthroscopic debridement groups concerning the VAS and OX-12 scores at the first visit although VAS and OX-12 scores had decreased in correlation to each other. This state of wellness lasted for 2 years but reached the same average values as the control group in the following year. There was no statistically significant difference concerning these values at the 3rd, 4th and 5th follow up visits (p>0,05) (Tables 5 and 6)

As a result, despite an improvement in clinical symptoms such as pain that starts at the 6th month and lasts for two years in viscosupplementation and debridement patients, there was no positive effect on the degenerative process as evidenced by radiological deterioration and the time until knee arthroplasty was not affected.

Discussion

This study aims to investigate the efficacy of NSAIDs, viscosupplementation and arthroscopic debridement which are frequently used for the

treatment of knee osteoarthritis, and to find out if they are effective in prolonging the time until arthroplasty. For this purpose, data was gathered from the patients and their medical records, and the patients were divided into three groups consisting of patients who were given only NSAIDs, patients who were given viscosupplementation, and patients who underwent arthroscopic debridement. Our study is the first to investigate the effects of these three treatment modalities on knee survival. Patients who were given viscosupplementation in addition to arthroscopic debridement and those who received more than one of these treatments were excluded from the study to achieve homogeneity.

When the groups were compared for age, obesity, gender, diabetes, smoking, and their VAS and OX-12 scores in the first admission, no statistically significant difference could be found (p>0,05). All patients were Grade 2 or 3 at the first admission and there was no significant difference concerning the distribution of patients (p>0,05).

Table-5. Distrubation of mean VAS scores according to treatment groups in the various control visit.

VAS Score	Control	Viscosupplementation	Arthroscopic debridement	F	p
First visit	5,0±2,5	5,5±2,4	5,1±2,0	0,619	0,540
6th month	6,0±2,9	4,3±1,4	4,6±2,0	7,890	**0,0001**
1st year	6,9±1,8	4,5±1,4	4,9±2,0	23,673	**0,0001**
2nd year	7,4±1,6	7,3±1,7	7,1±2,0	0,348	0,706
3rd year	8,1±1,5	8,0±1,6	8,1±1,6	0,064	0,938
4th year	8,3±1,4	8,2±1,5	8,2±1,5	0.499	0.608
5th year	8,4±1,6	8,5±1,5	8,3±1,6	0,201	0,818
Last visit	8,9±1,4	8,5±1,5	8,7±1,4	1.997	0,139
r	-	0,989 p>0,05		-	-
p	-			-	-

A total of 142 patients including the control group were evaluated in this study. 87 (61,3%) of the patients had undergone knee arthroplasty. The rate of operation due to total knee arthroplasty indication in the control group which consisted of patients who were given NSAID only, viscosupplementation groups, and the arthroscopic debridement group was 61,5%, 60,4%, and 61,9% respectively. There was no statistically significant difference concerning the average time between the first visit and the knee arthroplasty (p>0,05). The type of total knee prosthesis, postoperative alignment, and clinical outcomes were not evaluated as they were not the endpoints of this study.

The NSAIDs are the oldest and the most frequently used treatment for the primary knee osteoarthritis. Other analgesics and opioids can also be used for the treatment of pain [8]**.** NSAIDs were proven to be more effective than other analgesics in a study by Rasmussen et al in 2018 [12]**.** Weight control,

electrical stimulation, physiotherapy agents, and glucosamines are other conservative methods**.** NSAID are strongly recommended for KLC grade-1 primary degenerative arthritis and KLC grade 2-4 cases by the AAOS [13]**.** The NSAIDs, their efficacy, and usage times were ignored as heterogeneous variables since the aim of this study was to investigate the efficacy of other procedures. This could be seen as a limitation that weakens the study. However, the reasons for this limitation are the contraindication for prolonged use of NSAIDs due to systemic toxicity such as hepatotoxicity, cardiotoxicity, gastric irritation, and bleeding, the necessity to alternate drugs those are ineffective for pain, different prescription habits and their combination with other analgesics.

Recent studies report that proinflammatory cytokine levels are increased in primary knee osteoarthritis due to the stimulation of the Substance-P fibers found in the synovia, periosteum, and the adipose tissue by tumor necrosis factor- and interleukin (IL)-6 accelerates the degenerative process [8].

Table-6. Distrubation of mean OX-12 scores according to treatment groups in the various control visit

OX-12 Score	Control	Viscosupplementation	Arthroscopic debridement	F	p
First visit	22,4 ± 5,7	24,5 ± 5,9	23,7 ± 5,7	1,658	0,194
6th month	26,0 ± 6,9	20,3 ± 6,5	20,6 ± 7,0	11.046	**0,0001**
1st year	28,9 ± 5,6	19,5 ± 5,5	19,8 ± 6,0	43.706	**0,0001**
2nd year	31,4 ± 6,8	29,3 ± 6,9	29,2 ± 7,0	1.306	0,274
3rd year	35,2 ± 5,5	35,0 ± 5,6	35,1 ± 5,6	0.019	0.984
4th year	38,3 ± 6,5	38,2 ± 6,6	38,2 ± 6,6	0.004	0,996
5th year	41,4 ± 3,5	41,5 ± 3,4	41,3 ± 3,7	0.082	0.927
Last visit	46,9 ± 2,7	44,5 ± 2,9	45,7 ± 2,7	9.378	**0.0002**
r	-	0,999		-	-
p	-	p>0,05		-	-

NSAIDs inhibit the arachidonic acid synthesis by binding to the cyclooxygenase (COX) enzyme which in turn, inhibits inflammation and alleviates the pain indirectly**.** Gastric bleeding secondary to gastric irritation is the most important side effect of NSAIDs**.** The COX-1 enzyme is found in the platelets while COX-2 is found in the bones, muscles, and soft tissues. Selective COX-2 inhibitors cause less gastric irritation. None of the patients in this study used selective COX-2 inhibitors. The international consensus on the oral and topical use of these drugs was followed in this study [8]. Jersevar et al have proposed naproxen as the cheapest and most effective NSAID in their 2018 systematic review and meta-analysis [14]**.**

Viscosupplementation has gained widespread use in recent years. In the last few decades, the effect of intraarticular injections of corticosteroids, hyaluronic acid, and platelet-rich plasma (PRP) have been studied [6]. The hyaluronic acid injection has been reported to provide the most successful results by delaying, even stopping the degenerative process [2,5]**.** The intraarticular injection of hyaluronic acid promotes cartilage production and reduces the concentration of proinflammatory cytokines thus providing an anti-inflammatory effect **.** The authors stated that there is no evidence on the superiority of one type of hyaluronic acid on another [5]**.** Strand et al has published a meta-analysis and systematic review of literature on Hyalen-20, which has also been used in our study. The authors stated that high

molecular weight hyaluronic acid injections extracted from roosters or produced using genetic technology and approved by the US Food and Drug Administration (FDA) is efficient and safe [5]. Ayhan et al. have reported a medium level of wellbeing for an average of 24 weeks after intraarticular corticosteroid and PRP application but stated that there was no radiological improvement and the clinical improvement disappeared in the course of follow up. They also stated that the histopathologic effects of these treatment modalities are still unclear [4].

Campbell et al have published a systematic review and overlapping meta-analysis in 2016 and reported that hyaluronic acid and viscosupplementation are efficient and safe in the treatment of knee osteoarthritis and the clinical improvement becomes evident in the 26th week [9]. A similar improvement was detected around 26th week in a study involving 4,866 patients from 29 studies [5]. Jevsevar et al, in their systematic review of studies with a high level of evidence, reported only one randomized, prospective, double-blind study on this subject which did not find any statistically significant differences between placebo and hyaluronic acid [10].

The aim of arthroscopic joint cartilage debridement, which is also called arthroscopic abrasion arthroplasty, is to obtain a smoother surface by shaving the joint cartilage or to avoid fibrillation and softening of the cartilage by shrinking it using radiofrequency. This technique was popularized by Johnston in the 1980s. [15,1]. The microfracture technique, which was developed by Rodrigo et al, involves the excision of the cartilage until a spongious bone is exposed in osteochondral defects and drilling into this bleeding area using special awls in addition to arthroscopic debridement. Multipotent cells are expected to migrate into these holes and the area of the chondral defect will heal by itself as a result of chondrofication. The patients are asked not to bear weight on the operated knee for 6-8 weeks [13].

Several studies conducted in the last two decades report successful clinical and functional outcomes with arthroscopic debridement in primary osteoarthritis of the knee. There was a negative correlation between the degree of degeneration and the success of chondroplasty in arthroscopic debridement reported. Steadman et al reported successful results in 87% of arthroscopic debridement patients in 2013 [7]. In our study, VAS and OX-12 scores showed statistically correlated changes starting at 6 months and this improvement in pain and function lasted for 2 years. However, radiological deterioration continued.

It is not known whether the clinical improvement observed as a result of arthroscopic debridement is caused by the lavage and the mechanism is not still clear. Ike et al have compared arthroscopic lavage to NSAID treatment and found a 36% improvement in the NSAID group vs 62% improvement in the arthroscopic lavage group at the 12th week [16]. On the other hand, Chang et al found no statistically significant difference in their 1993 study where arthroscopic debridement and arthroscopic lavage were compared [17]. The results of arthroscopic debridement and microfracture technique are reported to be similar and between 50% and 65% [18]. Krüger et al. in their study where 162 patients underwent arthroscopic debridement and followed up for 40 months, stated that debridement did not contribute to cartilage healing and the inflammatory mediators released as a result of microfracture technique increased cartilage degeneration although a state of wellbeing which lasted for approximately one year was achieved [15]. In 2007, Steadman et al claimed that arthroscopic debridement prolonged knee survival for up to 10 years [11]. Spahn et al, in their meta-analysis published in 2013 where 30 studies with 1512 citations were evaluated, reported good or perfect results in 60 % of the patients. The authors have proposed that arthroscopic debridement delayed the time to arthroplasty, in other words, increased knee survival for 42,7 months [19]. We found that 69,1% of the patients who underwent arthroscopic debridement needed total knee arthroplasty in 6,0±2,1 years and knee survival was 38,1% in this group. In our study, the VAS scores of 42 patients who underwent arthroscopic debridement and/or microfracture technique dropped significantly which continued for approximately two years. None of the patients had any radiological improvements (increase in joint space, a decrease in the number of marginal osteophytes or subchondral cysts, etc.) throughout this period. On the other hand, arthroscopic debridement and microfracture technique did not have any statistically significant effect on the time until arthroplasty ($p>0,05$).

The foremost limitation of this retrospective cohort study is the lack of a double-blinded control, randomization, and prospective study design. Another limitation is the fact that different kinds of NSAIDs was used and for different periods in all groups. Some patients who were radiologically grade-4 did not want to undergo surgery due to fears of unsuccessful results or complications and other social reasons. This increases the knee survival period. Kaplan-Meier survival curves were

not used as this is not a prospective study. However, the duration between the first visit and total knee arthroplasty can be important.

In the light of this study it can be concluded that although viscosupplementation using intraarticular hyaluronic acid and arthroscopic debridement with or without microfracture technique provides a clinical relief which starts in 6 months and lasts for 2 years, they do not prolong the duration until arthroplasty and as such, do not affect on knee survival. A very important point to keep in mind is the clarification of this point when informing the patients.

Acknowledgments

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Conflict Of Interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

References

1. Mora JC, Rene Przkora R, Cruz-Almeida Y. Knee osteoarthritis: pathophysiology and current treatment modalities. J Pain Res 2018; 11: 2189-2196. doi: 10.2147 /JPR. S154002.
2. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum 2014; 43(6): 701–712.
3. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, Mcalindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med 2015; 162(1): 46–54.
4. Campbell KA, Erickson BJ, Saltzman BM, Mascarenhas R. Bach Jr BR, Cole BJ, Verma NN. Is local viscosupplementation injection clinically superior to other therapies in the treatment of osteoarthritis of the knee: a systematic review of overlapping meta-analyses. J Arthros Rel Surg 2015; 31(10): 2036-2045.
5. Strand V, McIntayr LF, Beach WR, Miller LE, Block JE. Safety and efficacy of US approved viscosuplements for knee osteoarthritis: a systematic review and meta-analysis of randomized, saline-controlled trials. J Pain Res 2015: 8: 217-228.
6. Jevsevar DS. Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. J Am Acad Orthop Surg 2013; 21(9): 571–576.
7. Steadman Jr AJ, Maxwell RB, Brigg KK. An arthroscopic treatment regimen for osteoarthritis of the knee. Arthroscopy. 2007; 23(9): 948-955. doi: 10.1016/j.arthro.2007.03.097.
8. Rafanan BS Jr, Valdecañas BF, Lim BP, Malairungsakul A, Tassanawipas W, Shiyi C, Tse LF, Luong TK. Consensus recommendations for managing osteoarthritic pain with topical NSAIDs in Asia-Pacific. Pain Manag. 2018; 8(2): 115-128. doi: 10.2217/pmt-2017-0047. Epub 2017 Dec 18.
9. Campbell KA, Erickson BJ, Saltzman BM, Mascarenhas R. Bach Jr BR, Cole BJ, Verma NN. Is local viscosupplementation injection clinically superior to other therapies in the treatment of osteoarthritis of the knee: a systematic review of overlapping meta-analyses. J Arthros Rel Surg 2015; 31(10): 2036-2045
10. Jevsevar D, Donnelly P, Brown GA Cummins DS. Viscosupplementation for Osteoarthritis of the Knee. A Systematic Review of the Evidence. J Bone Joint Surg Am. 2015; 97-A: 2047-2060.
11. Steadman JR, Briggs KK, Matheny LM, Ellis HB.Ten-year survivorship after knee arthroscopy in patients with Kellgren-Lawrence grade 3 and grade 4 osteoarthritis of the knee. Arthroscopy. 2013; 29(2): 220-225.
12. Rasmussen S. NSAIDs are superior to paracetamol for osteoarthritic pain and function in a network meta-analysis. BMJ Evid Based Med 2018; 23(1): 40-41.
13. AAOS: American Academy of Orthopaedic Surgeons. Treatment of osteoarthritis of the knee: Evidence-based guideline. 2nd edition. American Academy of Orthopaedic Surgeons, Rosemont 2013.
14. Jevsevar DS, Shores PB, Mullen K, Schulte DM, Brown GA, Cummins DS. Mixed treatment comparisons for nonsurgical treatment of knee osteoarthritis: a network meta-analysis. J Am Acad Orthop Surg 2018; 26: 325-336.

15. Krüger T, Wohlrab D, Birke A, Hein W. Results of arthroscopic joint debridement in different stages of chondromalacia of the knee joint. Arch Orthop Trauma Surg 2000; 120(5-6): 338-342.
16. Steadman Jr AJ, Maxwell RB, Brigg KK. An arthroscopic treatment regimen for osteoarthritis of the knee. Arthroscopy. 2007; 23(9): 948-955.
17. Chang RW, Falconer J, Stulberg SD, Arnold WJ, Manheim LM, Dyer AR. A Randomized, controlled trial of arthroscopic surgery versus closed-needle joint lavage for patients with osteoarthritis of the knee. Arthritis Rheum. 1993; 36(3): 289-296.
18. Law GW, Lee KJ, Soong J, Lim JWS, Zhang KT, Tan AHC. Arthroscopic debridement of the degenerative knee – Is there still a role? Asia Pac J Sports Med Arthrosc Rehabil Technol 2019; 15: 23–28. doi: 10.1016/j.asmart.2018.11.003.
19. Spahn G, Hofmann GO, Klinger HM. The effects of arthroscopic joint debridement in the knee osteoarthritis: results of a meta-analysis. Knee Surg Sports Traumatol Arthrosc 2013; 21(7): 1553-61. doi: 10.1007/s00167-012-2169-1.

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Investigation of Nulliparous Women's Attitudes Toward Fertility and Childbearing

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Review Article

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ABSTRACT

The aim of this study is to determine the attitudes of nulliparous women toward fertility and childbirth.
The research was carried out as a cross-sectional descriptive method with improbable sampling technique. Recruitment for participation in the study took place with power analysis and consisted of 213 nulliparous women who had never been pregnant before. Data were collected with the Personal Information Form and the Attitudes Toward Fertility and Childbearing Scale.
54% of the women are between the ages of 19-26 and the mean age is 26.51±5.19. It was determined that 76.5% of the women were married for 1-3 years and 65.7% of them used contraception. The total score of the Attitudes Towards Fertility and Childbearing Scale is 69.54±8.28, and the mean subscale score current obstacle 21.57±7.08; importance in the future 28.42±4.63; female identity is 19.55±3.82. It has been determined that women have a positive attitude to fertility and childbearing. In comparison with the total score of the scale and the variables, it was determined that there was a significant difference between variables of age, occupation status, spouse's age, spouse's occupation status, spouse's smoking status, consanguineous marriage, family type, financial status, spouse's age at marriage and mean value of total scale score.
The fact that nulliparous women's attitudes to fertility and childbearing are affected by many factors such as age, occupation status, spouse's age shows that there are many variables that should be considered during the evaluation of nulliparous women by midwives. It is very important for pregnancy planning that women in the preconceptional period have positive attitudes to fertility and childbearing.

Keywords: Nullipara, Fertility, Childbirth, Attitude

Nulipar Kadınların Doğurganlığa ve Doğuma Yönelik Tutumlarının İncelenmesi

Süreç

Geliş: 17/03/2023
Kabul: 27/09/2023

ÖZ

Bu çalışmanın amacı doğum yapmamış kadınların doğurganlığa ve doğuma ilişkin tutumlarını belirlemektir.
Araştırma olasılık dışı örnekleme tekniği ile kesitsel betimsel yöntem olarak gerçekleştirilmiştir. Araştırmaya katılım güç analizi ile gerçekleştirilmiş ve daha önce hiç hamile kalmamış 213 nullipar kadın katılmıştır. Veriler Kişisel Bilgi Formu ve Doğurganlığa ve Çocuk Doğurmaya İlişkin Tutum Ölçeği kullanılarak toplanmıştır.
Kadınların %54'ü 19-26 yaş aralığında olup yaş ortalaması 26,51±5,19'dur. Kadınların %76,5'inin 1-3 yıldır evli olduğu, %65,7'sinin gebeliği önleyici yöntem kullandığı belirlendi. Doğurganlığa ve Çocuk Doğurmaya Yönelik Tutum Ölçeği toplam puanı 69,54±8,28 olup, alt ölçek mevcut engel puan ortalaması 21,57±7,08; gelecekte önemi 28,42±4,63; kadın kimliği 19,55±3,82'dir. Kadınların doğurganlık ve çocuk doğurma konusunda olumlu tutuma sahip oldukları belirlendi. Ölçeğin toplam puanı ve değişkenler karşılaştırıldığında yaş, meslek durumu, eşin yaşı, eşin meslek durumu, eşin sigara içme durumu, akraba evliliği, aile tipi, maddi durum, eşin evlenme yaşı ve toplam ölçek puanının ortalama değeri.
Doğum yapmamış kadınların doğurganlık ve çocuk doğurma konusundaki tutumlarının yaş, meslek durumu, eş yaşı gibi birçok faktörden etkileniyor olması, doğum yapmamış kadınların ebeler tarafından değerlendirilmesi sırasında dikkate alınması gereken birçok değişkenin olduğunu göstermektedir. Prekonsepsiyonel dönemdeki kadınların doğurganlığa ve çocuk sahibi olmaya yönelik olumlu tutumlara sahip olmaları gebelik planlaması açısından oldukça önemlidir.

Anahtar Sözcükler: Nulipar, Doğurganlık, Doğum, Tutum

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Introduction

One of the most important choices for couples is the decision to become a parent. Although the decision to become a parent is thought to begin before pregnancy occurs after marriage, it is a fact that couples at duration of marriage clarify before marriage[1]. Because with the couple's decision to become a parent, the guiding roles that will support their children's basic needs and emotional needs in development will be added into their own responsibilities.[1,2]. Economic, social, emotional, and individual factors in parenthood roles will also affect the first child decision[3]. Beliefs, attitudes, and motivational factors are added to other factors affecting this decision[4]. Besides, due to the increase in the responsibilities of women compared to men, the concept of late motherhood appears[5]. Especially in traditional societies, while the concept of motherhood is seen as a complement to femininity and a source of happiness[6], not being a mother is expressed as a deficiency[5]. Despite this situation, radical changes in women's lives can cause them to postpone their decision to become a mother or not to be a mother. Among the reasons why women postpone motherhood, which means the role and status that affect their decisions, can be counted as the financial freedom they have gained by taking an active role in working life and the freedom in their own choice decision[7]. Generally, decreases in birthrate are inevitable because of postponing motherhood or the decision of not wishing to be a mother. Due to the factors affecting the childbearing, births have tended to decrease in the last 30 years and the elderly population has started to increase[8].

According to the data of the Turkish Statistical Institute (TUIK), while the total birthrate was 2.42 children per woman in the world in 2021, this rate was determined as 1.70 in our country[9]. For many countries, the falling birthrate is seen as a worrying situation. The economic uncertainties are among the reasons for this decline[10]. When reasons such as uncertainty in business life, temporary employment, unemployment and future anxiety are added to economic uncertainty, couples delay their decisions to become parents[10–12]. In addition to these factors affecting fertility, future scenarios resulting from negative events in the past are also reported to affect fertility[13].

Assuming that the birthrate is one of the important development indicators of a country, defining the reasons for the decline will be beneficial in taking precautions for the birthrate. It is thought that determining the Attitudes towards Fertility and Childbearing of nulliparous women delayed pregnancy will provide information on the causes of the birthrate tending to decrease. Birthrates tending to decrease not only in our country but also all over the world, are in the center of attention of the scientific world. When we look at the literature review, we mostly come across studies that show economic uncertainty causes fertility delays[10–13]. However, it should not be ignored that the delay in fertility is not limited to economic reasons but may be due to personal reasons[14]. For this reason, the research was planned to examine the attitudes of nulliparous women to fertility and childbearing by focusing on the decrease in the birthrate.

Research question

1. Do socio-demographic characteristics of nulliparous women affect their attitudes to fertility and childbearing?
2. Does being nullipara affect attitudes to fertility and childbearing?

Limitations (If exist)

The findings obtained from this study cover only the nulliparous women included in the study and cannot be generalized to all women.

Material and Method

The Objective and Type of This Research:

The research was conducted as a cross-sectional and descriptive study with the improbable sampling method to determine the attitudes of nulliparous women to fertility and childbearing.

Place and Time of Research:

It was conducted on nulliparous women who applied to the Obstetrics and Gynecology Polyclinics between 10.05.2022 and 30.07.2022 in a state hospital and a university hospital in Tokat province.

Population and Sample

G*Power 3.1.9.7 program was used to determine the sample of research. The medium effect size suggestion of Cohen (1988) was taken into consideration, and it was determined by taking 80% (1-β=0.80) power and 5% (α=0.05) margin of error [15]. As a result of the calculation, 213 nulliparous women were included in the study. According to the post-hoc analysis performed at the end of the study,

80% power (1-β=0.808), 5% (α=0.05) and medium effect size (f2=0.038) were reached with 213 women.

Inclusion criteria in the study.

- In the age group of 19-49
- Able to read and write.
- Living in the city center
- Never been pregnant before (nulliparous)
- No perception and communication problems
- Agreed to participate in the research.

Exclusion criteria for the study:

Adolescent women and women who did not agree to participate were not included.

Data Collection Tools:

Personal information form: In the form created by the researchers by analyzing the literature[16,17] there are 21 questions containing the socio-demographic information of the mothers (such as age, education, occupation status, spouse's occupation status).

Attitudes To Fertility and Childbearing Scale (AFCS): The Attitude to Fertility and Childbearing Scale was developed by Söderberg and her friends in 2013 to evaluate and compare the attitudes of women who have not yet become mothers-oriented fertility and childbearing, and the second version was published in 2015 by developers [16]. Turkish validity and reliability of it was done by Damar and Bolsoy in 2021. The original scale consists of 3 sub-dimensions (importance for -7 articles, hindrance at present -9 articles, and female identity -5 articles) with a total of 21 articles. The scale is a 5-point Likert type (strongly disagree, disagree, neither agree nor disagree, agree, completely agree). There is no reverse coding in the scale items. The Kaiser Meyer-Oklin (KMO) value for the sample adequacy of the original scale was found to be 0.945, and the Barlett test was found to be statistically significant for adequacy and factorization. The minimum score is 21 and the maximum score is 105, and the higher the score, the higher the attitude towards fertility and childbearing. In the validity analysis of the original scale; internal consistency and reliability of Cronbach's Alpha coefficients subscale and total scale value were reported between 0.862 and 0.945. In our study, the Cronbach's Alpha value of the total scale was 0.75.

Ethical Aspect of Research:

Every stage of the research was carried out in accordance with ethical principles. The study was conducted in accordance with the Principles of the Declaration of Helsinki. Before starting the application, necessary permissions were obtained from Tokat Gaziosmanpaşa University Social and Human Sciences Research Ethics Committee (dated 27.04.2022, decision number E-33490967-044-158700), Tokat Provincial Health Directorate (dated 10.05.2022, E-87064461-044) and Tokat Gaziosmanpaşa University Health Research and Application Center Directorate (dated 05.05.2022, numbered E-72843479-044-160527). While the women who met the inclusion criteria were invited to participate in the study, the Informed Consent Form was read, and their consent was obtained. The decision about whether to participate in the research was left to the women, and their voluntariness was taken into consideration.

Analysis of Data

The data obtained in the research were evaluated in the Statistical Package for Social Sciences (SPSS) 24.0 package program. Descriptive statistical analyses (number, percentage, mean, standard deviation, maximum, and minimum) were used in the evaluation of the data. Considering the normality analysis Kolmogorov Smirnov and the skewness- kurtois values being in the range of ±2, it was determined that the data obtained showed a normal distribution. The t test was used for the difference between the two means, and the one-way analysis of variance was used for more than two independent groups, and the error level was accepted as 0.05. Posthoc analysis was performed to determine between which groups the significance was formed (Tukey test). In addition, multiple linear regression was applied to the variables that were thought to influence the scale total score.

Findings

In Table 1 the distribution of the total and sub-scale means scores of the nulliparous women participating in the study on the Attitudes to Fertility and Childbearing Scale (AFCS) is given.

Table 1: Comparison of Nulliparas' AFCS Total Score and Sub-scale Score Means (*N*=213)

Scales	X̄	SS	min	max	Cronbach alpha
AFCS *	69,54	8,28	46	96	0,75
Hindrance at present	21,57	7,08	9	37	0,90
Importance for future	28,42	4,63	10	35	0,89
Famele identity	19,55	3,82	5	25	0,88

*AFCS: Attitudes Toward Fertility and Childbearing Scale

It can be found that the total mean score of the Nulliparas' AFCS is 69.54±8.28, and the highest score that could be obtained from the scale was 105 and according to this finding, nulliparas tend to fertility and childbearing above the average. The mean scores of the AFCS sub-dimensions were determined as hindrance at present 21.57±7.08; importance for future 28.42±4.63; female identity 19.55±3.82. When the internal validity coefficient and reliability level of the AFCS were examined, it was found that the general reliability levels of the scale sub-dimensions were high (0.80<α<1.00), and the overall reliability level of the total scale was quite reliable (0.60<α<0.80)[18] (Table 1).

The comparison of the sociodemographic characteristics of the nulliparas in the study and the total and sub-scalescore averages of the AFCS are given in Table 2.

Table 2: Distribution and Comparison of Sociodemographic and Marriage Characteristics of nulliparous women and Total and Sub-Dimensional Scores of the AFCS (*N* = 213)

Specifications	n	%	Hindrance at present X̄ ±SS	Importance for future X̄ ±SS	Female identity X̄ ±SS	Total scale X̄ ±SS
Age						
19-26 age (1)	115	54,0	20,00±6,47	28,44±4,21	19,79±3,66	68,23±7,23
27-34 age (2)	83	39,0	23,14±7,35	28,70±4,51	19,69±3,64	71,53±8,69
35 age and above (3)	15	7,0	24,87±7,38	26,80±7,57	17,00±5,12	68,67±11,49
			6,863/0,001*	1,070/0,345*	**3,709/0,026***	**4,015/0,019***
			1-3	-	**1-3, 2-3**	**1-2**
Age Average	26,51±5,19 (min:19 – max:45)					
Education						
Primary (1)	30	14,1	16,60±6,05	31,10±3,42	22,53±2,11	70,23±7,06
Secondary (2)	40	18,8	17,68±5,77	29,38±3,69	20,88±3,01	67,93±5,68
High School (3)	49	23,0	20,96±6,61	28,47±4,04	19,33±3,99	68,76±8,53
University (4)	94	44,1	25,13±6,23	27,15±5,17	18,16±3,78	70,44±9,34
			22,047/0,000*	**6,790/0,000***	**14,084/0,000***	1,091/0,354*
			1-3, 1-4	**1-4, 2-4**	**1-3, 1-4, 2-4**	-
Occupation status						
Working	90	42,3	25,69±6,49	27,66±5,05	18,40±3,94	71,74±9,96
Not Working	123	57,7	18,55±5,88	28,99±4,22	20,40±3,52	67,94±6,38
			8,235/0,000**	**-2,096/0,037****	**-3,891/0,000****	**3,174/0,002****
Spouse's age						
19-27 age (1)	84	39,4	19,92±6,44	28,26±4,39	19,52±3,65	67,70±6,96
28-36 age (2)	111	52,1	22,47±7,44	28,55±4,42	19,79±3,74	70,81±8,60
37 age and above (3)	18	8,5	23,72±6,36	28,44±6,79	18,22±4,89	70,39±10,60
			4,132/0,017*	0,092/0,913*	1,314/0,271*	**3,549/0,030****
			1-2	-	-	**1-2**
Spouse's age average	29,28±4,71 (min:19-max:45)					
Spouse's education status						
Primary (1)	18	8,5	17,06±6,03	29,17±5,46	22,11±2,78	68,33±6,78
Secondary (2)	32	15,0	16,94±6,40	31,44±3,20	22,22±2,01	70,59±7,40
	81	38,0	21,33±6,41	27,93±4,07	18,79±4,14	68,05±8,05

High School (3)	82	38,5	24,60±6,70	27,59±4,98	18,71±3,54	70,89±8,95
College/University (4)						
			14,290/0,000*	**6,320/0,000***	**11,857/0,000***	1,924/0,127*
			1-4, 2-3, 2-4	**2-3, 2-4**	**1-3, 1-4, 2-3, 2-4**	-
Spouse's Occupation status						
Working	204	95,8	21,61±7,19	28,47±4,71	19,60±3,87	69,68±8,42
Not working	9	4,2	20,56±3,87	27,56±1,87	18,44±2,06	66,56±3,08
			0,762/0,463**	1,286/0,221**	1,563/0,147**	**2,636/0,020****
Spouse's smoking status						
Smoking	137	64,3	19,56±6,54	28,66±4,59	19,92±3,90	68,14±7,06
Nonsmoking	76	35,7	25,18±6,59	28,01±4,70	18,89±3,61	72,09±9,66
			-5,990/0,000**	0,972/0,332**	1,885/0,061**	**-3,132/0,002****
Consanguineous marriage						
Yes	39	18,3	17,51±4,76	29,18±3,97	20,97±2,93	67,67±3,84
No	174	81,7	22,48±7,20	28,26±4,76	19,24±3,93	69,97±8,93
			-5,288/0,000*	1,123/0,263*	**3,125/0,003***	**-2,518/0,013****
Type of Family						
Nuclear	165	77,5	21,88±7,48	28,60±4,70	19,62±3,95	70,10±8,93
Extended	48	22,5	20,48±5,39	27,83±4,36	19,33±3,35	67,65±5,14
			1,445/0,152**	1,009/0,314**	0,496/0,621**	**2,415/0,017****
Perception of financial status						
Bad (1)	33	15,5	15,70±5,72	31,00±3,87	22,00±2,22	68,70±6,28
Satisfactory (2)	114	53,5	20,66±6,15	27,90±4,78	19,37±3,77	67,93±7,60
Excellent (3)	66	31,0	26,08±6,48	28,05±4,34	18,65±4,07	72,77±9,40
			33,523/0,000*	**6,349/0,002***	**9,414/0,000***	**7,819/0,001****
			1-2, 2-3, 1-3	**1-2, 1-3**	**1-2, 1-3**	**1-3, 2-3**
Place of Residence						
City	119	55,9	23,74±7,29	27,80±5,04	18,82±4,15	70,35±9,54
District	67	31,5	18,57±6,03	29,51±3,95	20,67±2,91	68,75±6,92
Countryside	27	12,6	19,44±5,04	28,52±3,87	20,04±3,64	68,00±4,23
			14,450/0,000*	2,979/0,053*	**5,524/0,005***	1,351/0,162**
			1-2, 1-3	-	**1-2**	-
Marriage duration						
1-3 years	163	76,5	21,11±7,04	28,60±4,53	19,60±3,95	69,30±8,33
4-6 years	32	15,0	22,94±7,20	28,03±4,80	19,84±2,98	70,81±8,38
7 year and above	18	8,5	23,28±6,99	27,61±5,32	18,67±4,01	69,56±7,92
			1,470/0,232*	0,501/0,607*	0,583/0,559*	0,443/0,643**
Average of marriage duration			2,79±2,63 year (min:1 – max:17)			
Marriage age						
15-20 age (1)	56	26,3	19,00±6,68	28,61±4,18	20,32±3,22	67,93±6,56
21-26 age (2)	108	50,7	21,69±6,42	28,31±4,41	19,46±3,92	67,45±8,52
27 age and above (3)	49	23,0	24,24±7,94	28,49±5,59	18,88±4,15	71,61±9,19
			7,649/0,001*	0,083/0,920*	1,942/0,146*	2,637/0,074**
			1-2, 1-3	-	-	-
Average of marriage age			23,69±4,19 age (min:15 – max:41)			
Spous' Marriage age						
17-22 age (1)	20	9,4	19,50±5,82	27,30±3,75	19,20±3,31	66,00±4,51
23-28 age (2)	142	66,7	21,13±7,14	28,39±4,66	19,75±3,78	69,27±8,32
29 age and above (3)	51	23,9	23,59±7,02	28,98±4,83	19,14±4,14	71,71±8,83
			3,263/0,040*	0,961/0,384*	0,579/0,561*	**3,732/0,025****
			1-3	-	-	**1-3**
Average of spouse' marriage age			26,49±3,57 age (min:17 – max:37)			
Contraception						
Yes	140	65,7	21,75±7,87	28,48±4,75	19,99±3,79	70,21±8,60
No	73	34,3	21,22±5,26	28,33±4,41	18,73±3,76	68,27±7,53
			0,585/0,559**	0,224/0,823**	**2,305/0,022****	1,628/0,105**

Contraception method						
Pill (1)	25	11,7	26,96±5,37	25,32±4,43	17,08±3,66	69,36±10,22
Intrauterine device (2)	44	20,7	18,16±8,15	30,64±4,06	22,27±1,95	71,07±8,46
Condom (3)	43	20,2	25,14±6,46	27,02±4,37	18,42±3,98	70,58±9,16
Injection(4)	5	2,3	19,20±7,98	29,20±4,91	19,80±2,77	68,20±6,18
Withdrawal (5)	23	10,8	17,17±6,06	30,35±4,42	21,74±3,01	69,26±6,48
Nonuse (6)	73	34,3	21,22±5,26	28,33±4,41	18,73±3,76	68,27±7,53
			11,224/0,000* **1-6, 3-6, 1-2**	**6,649/0,000*** **1-6, 1-2, 2-3**	**11,935/0,000*** **2-6, 5-6, 1-2**	0,806/0,547* -
TOTAL	**213**	**100,0**				

*One-Way Anova, **Independent Sample t test, AFCS: Attitudes to Fertility and Childbearing Scale

According to the nulliparous women's AFCS sub-scale of "Hindrance at present", it was determined that hindrance at present score average of women is higher whose specifications are 35 years and above, university graduated, working, spouse's age 37 years and above, spouse's education status university, working spouse, nonsmoking spouse, no consanguineous marriage, nuclear family type, excellent financial status, living in the city, married for 7 years or more, marriage age 27 years and above, spouses age 29 years and above, using contraception, using pills as contraception method. According to the comparison between hindrance at present sub-scale and the variables; it was determined that there was a significant difference (p<0.05) between specification of age, education status, Occupation status, spouse's age, spouse's education status, spouse's smoking status, consanguineous marriage, financial status, place of residence, marriage age, spouse's marriage age, contraception method and the current obstacle score averages (Table 2).

With respect to the Nulliparous women's AFCS sub-scale of " Importance for future", ,it was determined that the importance in the future score average of women is higher whose specifications are age between 27-34 years, primary school graduate, not working, spouse's age between 28-36, spouse's education status secondary school, working spouse, smoking spouse, consanguineous marriage, nuclear family type, bad financial status, living in district, marriage duration 1-3 years, marriage age 15-20, spouse's marriage age 29 years an above, using contraception, using contraception method of intrauterine device .

According to the comparison made between the sub-scale of "Importance for future" and the variables, it was determined that there was a significant difference (p<0.05) between the education status, occupation status, spouse's education status, financial status, the contraception method used and importance in the future score averages (Table 2).

From Nulliparous women's AFCS the sub-scale of "Female identity ", it was determined that Female identity score average of nulliparous women is higher whose specification of age between 19-26, primary school graduates, not working, spouse's age between 28-36, spouse' education status secondary education, working spouse, smoking spouse, consanguineous marriage, nuclear family type, bad financial status , living in a district, marriage duration 4-6 years, marriage age 23-28 years, using contraception, using contraception method of intrauterine device.

According to the comparison made between the sub-scale of female identity and the variables, it was determined that there was a significant difference (p<0.05) between age, education status, Occupation status, spouse's educational status, consanguineous marriage status, income level, place of residence, using contraception, using type of contraception and Female identity mean score (Table 2). In regards to the Nulliparous women's AFCS total score; it was determined that the women's mean total score of the scale was higher whose specifications of age between 27-34, university graduates, working, spouse's age between 28-36, spouse's education status university graduates, working spouse, spouse non-smoking, no consanguineous marriage, nuclear family type, excellent financial status, living in city, marriage duration 4-6 years, marriage age 27 years and above, spouse's marriage age 29 years and above, using contraception, using contraception method of intrauterine device . In reference to the comparison between the scale total score average and the variables, there was a significant difference between age, occupation status, spouse's age, spouse's occupation status, spouse's smoking status consanguineous marriage, family type, financial status, spouse's age at marriage, and scale total score averages. (p<0.05) was determined (Table 2).

Table 3: The Interaction between the Total Score of AFCS and Independent Variables

Independent Variables	B	Std.Error	p	95% CI	
				Lower	Upper
Age	***-3,231***	***1,222***	***0,008***	***-0,807***	***0,969***
Occupation status	-0,616	1,544	0,690	-3,660	2,428
Spouse's Age	0,229	0,311	0,463	-0,384	0,842
Spouse's Occupation status	-2,213	2,993	0,460	-8,115	3,688
Spouse's Smoking Status	**3,128**	**1,313**	***0,018***	**0,539**	**5,717**
Consanguineous marriage	-0,465	1,637	0,777	-3,694	2,764
Type of Family	-0,485	1,701	0,763	-3,421	2,709
Financial status	0,960	1,018	0,347	-1,046	2,967
Spouse's Marriage age	0,345	0,279	0,217	-0,204	0,895
R= 0,341 R^2 = 0,117	F=2,975		***p=0,002***		

It was determined that these variables in the model created according to the multiple linear regression analysis performed with the variables that are thought to influence the total score of the AFCS have an effect on fertility and childbearing in nulliparous women (p=0.002; p<0.05). Considering the significance tests of the regression coefficients, age and spouse's smoking status were found to be significant predictors of fertility and childbearing (p<0.05) (Table 3).

DISCUSSION

One of the most important choices for couples is the decision to become a parent. In the literature, it has been stated that the first baby is a very important factor for couples in fertility and reproductive decisions[19]. The reason for this is that the roles of womanhood and motherhood are complementary to each other, especially in patriarchal families[20]. This research was conducted to determine the attitudes of nulliparous women to fertility and childbearing.

In our study, it was determined that the total scores of the nulliparous women on the AFCS were above the average. In addition, when the sub-dimensions of the scale were examined, it was determined that the sub-dimensions of hindrance at present, importance for future and femininity identity were above the average. When the scale scores are evaluated, it can be said that women tend to fertility and childbearing. In a study conducted in Turkey, stated that women have a desire to have four or more children [21]. In the study conducted with Swedish women, it was determined that there is a perception of having children as an aspect of social identity[19]. This study supports our literature study and shows that the role of womanhood is associated with motherhood in Turkish societies as well as in other societies. The common point of the studies is the excess of individuals who are married and have partners. In a further study, it was determined that women with a partner had high mean scores in the "importance for future" and "female identity" sub-dimensions[16].

While women may think that having children at a younger age is more ideal, there is a tendency to postpone childbearing. In a study conducted by Lampic and fri. (2006), on university students, it was determined that 28 years for women and 30 years for men are the ideal age to have a first child[22]. A similar result was obtained in our study, and the mean age of nulliparous women was 26.51±5.19 years. This result shows that similar attitudes exist not only in our country but also in different countries of the world. Likewise, in another study conducted by Tough and fri., (2007) on men and women who do not have children, it was stated that 47.8% of men and 44.5% of women pointed to the ideal parenthood age range of 25-29 years[23].

It was determined that the variables in the model created according to the multiple linear regression analysis performed with the variables that were thought to influence the total score of the AFCS had an effect on fertility and childbearing in nulliparous women. Considering the significance values of the regression coefficients, it is important to draw attention to this issue that age and spouse's smoking status, which are independent variables, were found to be significant predictors of fertility and childbearing. At the same time, when the scale sub-dimensions of "hindrance at present", " importance for future" and "female identity" were examined, it was determined that there was a significant relationship between sociodemographic variables such as age, marriage year, educational status and the sub-scale mean scores. However, it was determined that there was no significant

difference between the use of contraception method with the hindrance at present and importance in the future sub-scales, but only exist with the female identity sub-scale. This is thought to be since women use contraception methods as a symbol of femininity. in our study the comparison of the method of contraception used and the total score averages of the scale, it was determined that the highest average score was found in those who used the intrauterine device and the lowest score average was in the injection users. According to this result, it is seen that women's attitudes to childbearing are high even if they use contraceptive intrauterine devices.

In traditional societies with low education levels, the marriage age declines, the use of contraceptives decreases, and the number of births increases [21,24]. Since the distribution of the participants in our study in terms of education status is similar, it is thought that the difference between the use of contraception method is not significant. When the studies in the literature are examined, it is stated that as the education increases, the tendency of women to fertility and childbearing decreases. In addition, sociodemographic data (age, occupation status, marriage duration, etc.) are stated as factors affecting women's attitudes to fertility and childbearing[16,21,25,26]. According to our study results supported by the literature, considering that sociodemographic characteristics and financial status are factors in women's attitudes to fertility and childbearing, it can be said that the reasons for postponing motherhood, which is seen as a feminine role, may be individual diversity.

CONCLUSION AND RECOMMENDATIONS

It was determined that the Nullipara's total and sub-scale scores of the AFCS were above the average. In the analyzes made, it was determined that sociodemographic characteristics influenced fertility and childbearing. It is noteworthy that age and spouse's smoking status, which are independent variables, were found to be significant predictors of fertility and childbearing, and that there was a significant difference between the usage of contraception and the mean scores of the sub-dimensions of "hindrance at present", "importance for future" and "female identity".

In this manner, it is very important for women to have positive attitudes to fertility and childbearing in terms of pregnancy planning in preconceptionally period. Today for patriarchal societies, it is important to determine the attitudes of women to fertility and childbearing, since the roles of womanhood and motherhood are matched. The fact that nulliparous women's attitudes to fertility and childbearing are affected by many factors such as age, occupation status, spouse's age shows that there are many variables that should be considered during the evaluation of nulliparous women by midwives. In this context, women's attitudes toward fertility and childbearing will become more important in the future, considering the decreasing population growth. However, women's attitudes toward fertility and childbearing should be considered together with their spouses. Therefore, there is a need for more comprehensive studies involving spouses.

Conflict of Interest

There is no conflict of interest.

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Authorship Contribution

MHA, HÖ, DÇ; opinion/concept, design, supervision, DÇ: analysis. MHA, HÖ, DÇ; comment, writing, critical review. MHA, HÖ; resources, collecting data, literature search.

References

1. Doepke M, Sorrenti G, Zilibotti F. The economics of parenting. Annual Review of Economics 2019; 11(1): 55–84. https://doi.org/10.1146/annurev-economics-080218-030156
2. Vignoli D, Bazzani G, Guetto R, Minello A, Pirani E. Uncertainty and narratives of the future: a theoretical framework for contemporary fertility. In Schoen R (Ed.), Analyzing Contemporary Fertility. The Springer Series on Demographic Methods and Population Analysis 2021; 51: 25–47. Springer, Cham. https://doi.org/10.1007/978-3-030-48519-1_3
3. Sakman E. Gönüllü çocuksuzluk: Çocuk sahibi olmama kararının altında yatan faktörler ve karşılaşılan tepkiler hakkında bir derleme. Psikoloji Çalışmaları 2021; 41(1); 83–109. https://doi.org/10.26650/SP2020-0105
4. Mynarska M, Brzozowska Z. Things to gain, things to lose: perceived costs and benefits of children and ıntention to remain childless in Poland. Social Inclusion 2022;

10(3): 160–171. https://doi.org/10.17645/SI.V10I3.5377
5. Gezer Tuğrul Y. Toplumsal cinsiyet bağlamında kadınların annelik deneyimleri üzerine bir saha çalışması. Toplum ve Kültür Araştırmaları Dergisi 2019; 3: 71–90.
6. Arslan S, Okcu G, Margirit Coşkun A, Temiz F. Kadınların gebeliği algılama durumu ve bunu etkileyen faktörler. HSP 2019; 6(1): 179–192. https://doi.org/10.17681/hsp.432333
7. Zeybekoğlu Akbaş Ö, Dursun C. Toplumsal değişme sürecinde annelik serüveni: genç annelikten geç anneliğe geçiş. Akademik Hassasiyetler 2022; 9(20): 107–128. https://orcid.org/0000-0003-0407-5774.
8. Alçin Şahintürk D, Çelebi AK. Doğurganlık hızını arttırmaya yönelik kamu mali teşvikleri: Avustralya, Japonya, Danimarka, Fransa, Kanada ve Rusya analizi. Pamukkale University Journal of Social Sciences Institute 2021; 49: 69–47. https://doi.org/10.30794/pausbed.870493
9. TÜİK-Türkiye İstatistik Kurumu. TÜİK Haber Bülteni. In Türkiye İstatistik Kurumu Haber Bülteni 2022 https://data.tuik.gov.tr/Bulten/Index?p=Dunya-Nufus-Gunu-2022-45552
10. Lappegård T, Kristensen AP, Dommermuth L, Minello A, Vignoli D. The impact of narratives of the future on fertility intentions in Norway. Journal of Marriage and Family 2022; 84(2): 476–493. https://doi.org/10.1111/JOMF.12822
11. Comolli CL, Vignoli D. Spreading uncertainty, shrinking birth rates: A natural experiment for Italy. European Sociological Review 2021; 37(4): 555–570. https://doi.org/10.1093/esr/jcab001
12. Matysiak A, Sobotka T, Vignoli D. The great recession and fertility in Europe: A sub-national analysis. European Journal of Population 2021; 37(1): 29–64. https://doi.org/10.1007/S10680-020-09556-Y/FIGURES/6
13. Vignoli D, Minello A, Bazzani G, Matera C, Rapallini C. Narratives of the future affect fertility: evidence from a laboratory experiment. European Journal of Population 2022; 38(1): 93–124. https://doi.org/10.1007/S10680-021-09602-3/TABLES/4
14. Aşcı Ö, Gökdemir F. Doğurganlığa ve çocuk sahibi olmaya yönelik tutum ölçeğinin Türkçeye uyarlanması adaptation of attitudes toward fertility and childbearing scale to Turkish. Kocaeli Med J 2021; 10(1): 194–205.
15. Polit, D., & Beck, C. (2017). *Nursing research: Generating and assessing evidence for nursing practice* (10th ed.). PA: Lippincott Williams & Wilkins.
16. Söderberg M, Christensson K, Lundgren I, Hildingsson I. Women's attitudes towards fertility and childbearing – A study based on a national sample of Swedish women validating the Attitudes to Fertility and Childbearing Scale (AFCS). Sexual & Reproductive Healthcare 2015; 6(2); 54–58. https://doi.org/10.1016/J.SRHC.2015.01.002
17. Ali M, Alauddin S, Farida Khatun M, Maniruzzaman M, Mohammed Shariful Islam S. Determinants of early age of mother at first birth in Bangladesh: a statistical analysis using a two-level multiple logistic regression model. Journal of Public Health: From Theory to Practice 2021; 29: 1081–1087. https://doi.org/10.1007/s10389-020-01228-9/Published
18. Damar E, Bolsoy N. Doğurganlık ve çocuk doğurmaya yönelik tutum ölçeği Türkçe formunun geçerlik ve güvenirlik çalışması. International Anatolia Academic Online Journal Health Sciences 2021; 7(3): 1–34.
19. Kossakowska, K., & Söderberg, M. Psychometric properties and factor structure of the attitudes to fertility and childbearing scale (AFCS) in a sample of polish women. Current Psychology 2021; 40(7): 3125–3135. https://doi.org/10.1007/S12144-020-01004-8/TABLES/4
20. Bahtiyar-Saygan B, Sakallı-Uğurlu N. Development of attitudes toward voluntary childlessness scale and ıts associations with ambivalent sexism in Turkey. 2019; 40(17): 2499–2527. https://doi.org/10.1177/0192513X19860168
21. Eroğlu K, Koruk F, Koruk İ, Çelik K, Güner P, Kiliçli A. Women's reproductive behaviour and perspectives on fertility, and their modifying factors, in a Turkish province with a high fertility rate. The European Journal of Contraception & ReproductiveHealth Care 2021; 26(2): 139–147. https://doi.org/10.1080/13625187.2020.1857355

22. Lampic C, Svanberg AS, Karlstrom P-O, Tyden T. Fertility awareness, intentions concerning childbearing, and attitudes towards parenthood among female and male academics, Hum Reprod 2006; 21: 558-564. https://doi.org/10.1093/humrep/dei367
23. Tough S, Tofflemire K, Benzies K, Fraser-Lee N, Newburn-Cook C. Factors influencing childbearing decisions and knowledge of perinatal risks among Canadian men and women, Mat Child Health 2007; 11: 189-198. https://doi.org/10.1007/s10995-006-0156-1
24. Aly R, Aly M. The situation of egyptian women in childbearing and family planning and some related factors: A perspective of correspondence analysis. Universal Journal of Public Health 2023; 11(1): 14–26. https://doi.org/10.13189/ujph.2023.110103
25. Coutinho RZ, Golgher AB. Modelling the proximate determinants of fertility for Brazil: the advent of competing preferences. Revista Brasileira de Estudos de População 2018; 35(1): e0041. https://doi.org/10.20947/S0102-3098A0041
26. Lane SD, Burns RD, Fu Y, Golub R, Ivkov-Dzigurski A, Simeunovi´c VS. Determinants of fertility ıntentions of the women in Bosnia and Herzegovina—An example from the Semberija Region. Behavioral Sciences 2023; 13(5): 417. https://doi.org/10.3390/BS13050417