Cumhuriyet Medical Journal, 44(4): 390-396, 2022
DOI: http://dx.doi.org/10.7197/cmj.1215068

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

The Relationship between Fibroblast Growth Factor-23, Insulin-Like Growth Factor-1, Bone Mineral Density, Insulin Resistance, and Hyperandrogenemia in Polycystic Ovary Syndrome

Enver Çiftel[1,a*], Mehmet Fatih Kılıçlı[2,b], Serpil Çiftel [3,c],

[1] Department of Endocrinology and Metabolism, Sivas Numune Hospital, Sivas, Turkey, [2]Department of Endocrinology and Metabolism, Medipol University Hospital, Istanbul, Turkey ,[3]Department of Endocrinology, Erzurum Training and Research Hospital, Erzurum, Turkey,

**Corresponding author*

Research Article

History

Received: 06/12/2022
Accepted: 27/12/2022

ABSTRACT

Aims: The aim of this study was to find out the association between the Fibroblast Growth Factor-23 (FGF-23), Insulin-Like Growth Factor-1 (IGF-1), androgens, insulin resistance (IR), and bone mineral density (BMD) in patients with PCOS (Polycyctic Ovary Syndrome) and healthy controls is presented.

Materials and Methods: The FGF-23, IGF-1, and Homeostatic Model Assessment for Insulin Resistance were evaluated in 47 patients with PCOS and 26 healthy females, and BMD was evaluated only in the PCOS group. Then these parameters were compared between groups, according to the presence of IR and hyperandrogenemia.

Results: The mean FGF-23 was 137.55± 75.42 and 414.81 ± 53.02 (pg/ml), and mean IGF-1 was 28.41 ± 99.69 and 244.26 ± 58.99 (ng/ml) in patients with PCOS and healthy controls, respectively. In PCOS group, the FGF-23 was more significantly decreased in those with IR and amenorrheic. DEXA scores were found to be similar in PCOS group in terms of hyperandrogenemia and IR.

Conclusions: Our results revealed that FGF-23 levels decreased in patients with PCOS, which was particularly significant in patients with IR. According to our findings; the low level of FGF-23 in the PCOS group with IR suggests that this marker may also be associated with the complications of PCOS, but to clarify this hypothesis, this marker needs to be investigated.

Keywords: Polycystic Ovary Syndrome, Insulin Resistance, FGF-23

Polikistik Over Sendromunda İnsülin Rezistansı ve Hiperandrojenemi ile Serum FGF-23, IGF-1 Düzeyi ve Kemik Mineral Dansitesi Arasındaki İlişki

Süreç

Geliş: 06/12/2022
Kabul: 27/12/2022

ÖZ

Amaç: Çalışmamızın amacı; PCOS'lu hastalar ve sağlıklı kişilerde serum Fibroblast Büyüme Faktörü-23 (FGF-23) ve İnsülin benzeri büyüme faktörü (IGF-1) düzeyi, androjen düzeyleri, insulin rezistansı (IR) ve kemik mineral dansitesi (BMD) arasında ilişki olup olmadığını araştırmaktır.

Yöntem: Bu çalışmada 47 PCOS' lu ve 26 sağlıklı kadının FGF-23, IGF-1 değeri, HOMA-IR değeri çalışıldı Hasta grubunda BMD değerlendirildi. Ayrıca PCOS'lu hastalar insülin direnci ve hiperandrojenemiye sahip olup olmamasına göre bu parametreler yönünden kendi arasında karşılaştırıldı.

Bulgular: Bu çalışmada PCOS'lu hastaların FGF-23 değeri 137.55 ± 75.42 (pg/ml), IGF-1 değeri 28.41 ± 99.69 26 (ng/ml) iken kontrol grubunun FGF-23 değeri 414.81 ± 53.02 (pg/ml) ve IGF-1 değeri 244.±58.99 (ng/ml) idi. FGF-23 düzeyi IR ve amenoreik olan grupta daha düşük bulunmuştur. BMD ise hiperandrojenemi ve insülin direnci olup olmamasına göre farklılık göstermemiştir.

Sonuç: PCOS'lu hastalarda FGF-23 düzeylerinin azaldığı özellikle de insülin direnci ve amenoreik olan hastalarda daha düşük olduğu bulunmuştur. PCOS'lu hasta grubunda ve IR varlığında FGF-23'ün düşük seviyeleri bu markerin PCOS komplikasyonlarıyla ilişkili olabileceğini öngörmektedir. Ancak bu konunun aydınlatılabilmesi için daha fazla sayıda hasta içeren çalışmaların yapılması gerekmektedir.

Anahtar sözcükler:Polycystic Ovary Syndrome, Insulin Resistance, FGF-23

[a] *enver-ciftel@hotmail.com* *https://orcid.org/0000-0003-1431-5663*
[b] *mfatihkilicli@yahoo.com* *https://orcid.org/0000-0001-8962-7835*
[c] *serpilim2008@hotmail.com* *https://orcid.org/0000-0001-6962-4039*

*How to Cite:*Çiftel E, Kılıçlı MF, Çiftel S (2022) The Relationship between Fibroblast Growth Factor-23, Insulin-Like Growth Factor-1, Bone Mineral Density, Insulin Resistance, and Hyperandrogenemia in Polycystic Ovary Syndrome,Cumhuriyet Medical Journal, December2022, 44 (4): 390-396

Introduction

Polycystic Ovary Syndrome (PCOS) is a chronic endocrine and metabolic disease whose pathophysiology is unknown despite numerous clinical, laboratory, and experimental data [1]. PCOS is observed in 5%–10% of females in the reproductive period. PCOS have different clinical presentations, especially obesity, hyperandrogenemia, and insulin resistance (IR). The etiology of IR in PCOS has not been fully elucidated. IR may be due to decreased insulin receptors, antibodies to the receptors, or post-receptor defects. IR is independent of patients' adiposity, body fat topography and androgen levels [2]. According to research, increased insulin-like growth factor-1 (IGF-I) levels in PCOS patients is associated with IR. Increasing IGF-1 increases the number of luteinizing hormones (LH) receptors, thus increasing the binding capacity of LH. Accumulation of insulin stimulates GnRH and LH pulse secretion via influencing both amplitude and frequency [3]. LH and insulin interaction enhance steroidogenic acute regulatory enzyme and CYP450c17 mRNA expression [4]. High insulin levels cause IGF-1 to synergistically act with LH on theca cells. With a synergistic effect, P450 c 17 alpha enzyme activity increases, and ovarian androgen release increases[5].

IGF-1 acts in endocrine, paracrine, and autocrine ways. The main function of IGF-1 is the stimulation of osteoblastic function and bone formation. IGF-1 is found in many tissues, but circulating IGF-1 is produced in the liver and its release is controlled by the growth hormone. Its synthesis in osteoblasts is mainly under the control of parathyroid hormone (PTH). IGF-1 mediates the anabolic effects of PTH in bone. Estrogen increases transcription of IGF-1 in osteoblasts. The function of IGF-1 in osteoclasts is vague. IGF-1 receptors are also expressed in osteoclasts. In vitro, IGF-1 induces receptor activator of nuclear factor-kappa beta ligand (RANKL) synthesis. RANKL induction by IGF-1 can also cause increased bone resorption. Thus, IGF-1 has a dual role on bones, and bone resorption may explain its modest effect on bone mass increase.

Obesity, hyperandrogenism and higher estradiol levels are protective factors against bone loss. Patients with PCOS tend to be obese. A small portion of patients with PCOS present with a normal body mass index (BMI ≤ 25 kg/m2), and are classified as "lean PCOS". Recent research suggests that metabolic, hormonal, and hematological abnormalities are similar to women with "obese PCOS," however they are usually more subtle and less-severe [6].

Fibroblast Growth Factor-23 (FGF-23) is a 30 kilodalton protein secreted by osteoblasts that regulate mineral metabolism [7]. FGF-23 is secreted due to the increased phosphorus load and is important in maintaining normal serum phosphate levels. It also inhibits the sodium-phosphate (NaP-2b) cotransporter Type 2b, thereby reducing vitamin D-dependent phosphate absorption from the intestines [8,9]. It prevents the absorption of phosphorus in the diet by inhibiting the enzyme activity of 1-alpha-hydroxylase and blocking the synthesis of vitamin D.

This study aimed to determine how IR and hyperandrogenemia affect serum FGF-23 and IGF-1 levels in patients with PCOS and investigate the relationship between preserved bone mass in patients with PCOS and FGF-23 and IGF-1 levels.

Our study will clarify how the FGF-23 levels change in patients with PCOS, which has not been studied before in the literature and contribute to the elucidation of the cellular mechanisms of preserved bone mass in PCOS. If these mechanisms are related to decreased FGF-23 levels, then new studies on the bone protective effect of anti-FGF-23 therapy will be prepared in the future.

Materials and Methods

Our study is a cross-sectional study. A total of 47 patients, 21 with IR and 26 without IR, diagnosed with PCOS and admitted to the Endocrinology outpatient clinic, were included in this study. The control group consisted of 26 healthy individuals without any chronic disease. A venous blood sample taken for FGF-23 measurement from patients who applied to the clinic was placed in 5 ml biochemistry tubes with polypropylene gel. After the samples were taken, the serums were collected by centrifuging the tubes at 4000 rpm for 10 min on the same day (within 3 h). Serums were stored at - 80 °C for 2 months before analysis. From the serum samples on a working day, the FGF-23 level was studied with the enzyme-linked immunosorbent assay (ELISA) method in the Chemwell Awareness Technology, Inc ELISA device with the East biogoharm brand ELISA kit with catalog number CK-E90226.

For the measurement of IGF-1, the venous blood sample taken from the patients who applied to the clinic was placed in 5 ml biochemistry tubes with polypropylene gel. After the samples were taken, the serums were collected by centrifuging the tubes at 4000 rpm for 10 min on the same day (within 3 h). Serums were stored at −80 °C for 2 months before analysis. From the serum samples on a working day, it was studied using the ready-made commercial kits of the Siemens Immulite 2000 XPI brand auto-analyzer.

For the level of follicle-stimulating hormone, LH, prolactin, PTH, vitamin D, estradiol, total testosterone, and free testosterone, blood was taken from the antecubital vein and poured into 5 ml tubes with polypropylene gel. Blood samples were studied using Architect brand-ready commercial kits on Abbot Architect İ2000Sr auto-analyzer device.

Blood was taken from the antecubital vein for insulin, cortisol dehydroepiandrosterone sulfate, and SHBG levels and poured into 5 ml tubes with polypropylene gel. Blood samples were studied in the Siemens Immulite 2000 XPI auto-analyzer device using Immulite brand-ready-made commercial kits.Blood was

drawn from the antecubital vein for low-density lipoprotein (LDL), total cholesterol, triglyceride, blood urea nitrogen, creatinine, and calcium, phosphorus, and glucose levels and poured into 5 ml tubes with polypropylene gel. Blood samples were studied on the Roche Cobas 8000 C702 auto-analyzer. IR was determined by theHomeostatic Model Assessment for Insulin Resistance (HOMA-IR) method (HOMA-IR = Fasting Glucose (mg/dl) × Fasting Insulin (microU/ml)/405). Patients with HOMA-IR ≥2.5 were considered as positive for IR. Hyperandrogenism was accepted in the presence of clinical and biochemical signs of hyperandrogenism.

Statistical analysis

The obtained data in our study was added to the Statistical Package for the Social Sciences 14.0 program and the Mann Whitney-U test and correlation analysis were applied in the evaluation of the data since the parametric test assumptions were not fulfilled in the data evaluation (Kolmogorov-Smirnov). Our data are presented in the tables as arithmetic mean ± standard deviation, and the error level is taken as 0.05.

Results

In the comparison of the PCOS and control groups in terms of measured parameters only FGF-23 and phosphorus showed a significant difference ($p < 0.05$) between groups. FGF-23 was found to be lower and phosphorus higher in the PCOS group (Table 1). There were significant differences in terms of FGF-23, total cholesterol, LDL, triglyceride, muscle mass, and body weight in the comparison of patients with and without IR in the PCOS group ($p< 0.05$). Among these parameters, FGF-23 was the only parameter that was found to be higher in the group without insulin resistance, while the others were higher in the insulin resistant group (Table 2).

Table 1. Comparison of groups in terms of measured parameters

	PCOS (+) X ±S	Control X ±S	p
FGF-23 (pg/ml)	137.55 ± 75.42	414.81 ± 53.02	0.001*
IGF-1 (ng/ml)	228.41 ± 99.69	244 ± 58.99	0.462
Calcium (mg/dl)	9.6 ± 0.37	9.53 ± 0.38	0.584
Phosphorus (mg/dl)	3.85 ± 1.02	3.45 ± 0.59	0.047*
PTH (pg/ml)	46.67 ± 25.32	47.71 ± 13.33	0.420
SHBG (nmol/l)	56.47 ± 40.32	70.51 ± 52.84	0.359

*$p< 0.05$ is significant, PCOS: Polycystic Ovary Syndrome, FGF-23: Fibroblast Growth Factor-23, IGF-1: Insulin-Like Growth Factor-1, PTH: Parathyroid hormone, SHBG: Sex Hormone Binding Globulin

Table 2. Comparison of measured parameters in PCOS with and without IR

	PCOS		
	IR (+) X ±S	IR (–) X ±S	p
FGF-23 (pg/ml)	90.31 ± 67.2	175.7 ± 58.8	0.001*
IGF 1 (ng/ml)	229.0 ± 113.7	227.9 ± 88.6	0.965
PTH (pg/ml)	43.1 ± 23.9	49.5 ± 26.5	0.280
Phosphorus (mg/dl)	4.00 ± 1.42	3.72 ± 0.49	0.864
Triglyceride (mg/dl)	151.4 ± 87.3	77.1 ± 32.9	0.001*
LDL (mg/dl)	106.7 ± 34.5	80.46 ± 31.4	0.018*
Total cholesterol (mg/dl)	174 ± 35.2	150 ± 29.9	0.015*
FAT (%)	33.5 ± 11.6	27.1 ± 7.8	0.31
FAT Mass (kg)	28.3 ± 25.8	18.1 ± 8.66	0.089
Muscle Mass (kg)	46.5 ± 6.17	42.6 ± 3.16	0.025*
BMI (kg(m^2)	28.1 ± 6.62	25.3 ± 5.06	0.227
Weight (kg)	75.1± 17.9	64.1 ± 10.6	0.048*
Calcium (mg/dl)	9.68 ± 0.30	9.53 ± 0.41	0.130
Vertebral Z score	-0.15 ± 1.16	-0.47 ± 0.81	0.154
Femoral Z score	0.03±1.05	-0.23±0.57	0.256

*$P <$ 0.05 is significant

No difference was found in the comparison of dual-energy x-ray absorptiometry (DEXA) vertebral and femoral Z scores in PCOS group with and without IR. In the comparison of FGF-23, IGF-1, PTH, phosphorus,

calcium, SHBG, LDL, HDL, triglyceride, total cholesterol, fasting blood glucose, Fat, Fat-MASS, Muscle-MASS, BMI, waist circumference, hip circumference, waist/hip ratio, and weight with and without hyperandrogenemia in the PCOS group it was revealed that Fat-mass and phosphorus were higher in patients with hyperandrogenemia, whereas SHBG was lower. The difference in terms of other parameters was found to be insignificant. Also, DEXA scores were found to be similar in PCOS group in terms of hyperandrogenemia (Table 3).

Table 3. Comparison of measured parameters in PCOS group with and without Hyperandrogenemia

	PCOS		
	Hyperandrogenemia (+) X ± S	Hyperandrogenemia (–) X ± S	*p*
FGF-23 (pg/ml)	146.6 ± 76.81	111.0 ± 67.22	0.143
IGF-1 (ng/ml)	232.9 ± 99.51	214.0 ± 103.7	0.607
PTH (pg/ml)	44.92 ± 21.62	51.78 ± 34.61	0.826
Calcium (mg/dl)	9.605 ± 0.353	9.591 ± 0.448	0.912
Vitamin D (ng/ml)	17.86 ± 10.42	17.04 ± 9.203	0.836
Phosphorus (mg/dl)	4.026 ± 1.101	3.344 ± 0.484	0.005*
SHBG (nmol/L)	45.29 ± 23.50	86.23 ± 58.87	0.021*
Fasting Blood sugar (mg/dl)	90.40 ± 8.928	93.75 ± 19.37	0.922
HDL (mg/dl)	47.31 ± 12.01	56.41 ± 25.96	0.201
Triglyceride (mg/dl)	117.2 ± 78.25	90.16 ± 51.47	0.262
LDL (mg/dl)	96.00 ± 37.57	81.11 ± 24.65	0.11
Total cholesterol (mg/dl)	163.5 ± 34.64	152.8 ± 33.08	0.386
FAT (%)	31.63 ± 9.794	25.22 ± 10.00	0.055
FAT-MASS (kg)	24.66 ± 13.22	17.09 ± 12.22	0.047*
MUSCLE-MASS (kg)	45.06 ± 4.91	42.58 ± 5.35	0.105
BMI (kg/m^2)	27.15 ± 6.0	24.90 ± 5.53	0.168
Waist circumference (cm)	84.20 ± 10.4	79.08 ± 8.63	0.098
Hip circumference (cm)	100.8 ± 11.03	97.08 ± 10.56	0.491
Waist/Hip ratio	0.832 ± 0.070	0.820 ± 0.063	0.549
Weight (kg)	70.54 ± 15.00	64.91 ± 15.80	0.191
Vertebral Z score	−0.32 ± 0.97	−0.34 ± 1.07	0.874
Femoral Z score	−0.10 ± 0.90	−0.12 ± 0.60	0.741

*p< 0.05 is significant

In the PCOS group; FGF-23 was found to be lower in those with amenorrhea, IGF-1 was found to be similar (Table 4).

Table 4. Comparison of FGF-23 and IGF-1 in PCOS group with and without Amenorrhea

	PCOS		
	Amenorrhea (+) X ± S	Amenorrhea (–) X ± S	p
FGF-23 (pg/ml)	127.94 ± 76.53	154.50 ± 72.53	0.03*
IGF 1 (ng/ml)	221.96 ± 111.10	240.50 ± 75.55	0.305

* p< 0.05

Discussion

FGF-23 is a molecule primarily synthesized by osteocyte-osteoblasts in bone and acts by increasing phosphate excretion and decreasing vitamin D synthesis in the kidney. FGF-23 level was shown to be directly or indirectly affected by both systemic and local factors [10]. At high FGF-23 levels, bone mineralization is impaired, and may become fragile. This study investigated the relationship between IR, hyperandrogenemia, FGF-23, IGF-1, and BMD in patients with PCOS. Following the established hypothesis in planning the study, we found that the FGF-23 level in PCOS group was statistically significantly lower than the control group, but the effect of this difference on bones could not be evaluated, since DEXA could not be applied to the control group due to ethical reasons. There is only one study in the literature on the relationship between FGF-23 and PCOS, and in that study, unlike our study, no difference was found between PCOS and control groups in terms of FGF-23 levels [11].

IR is a condition characterized by impaired peripheral tissue response to the metabolic effects of insulin. Insulin has an antiphosphaturic effect by directly stimulating NaPi-II and increasing renal phosphorus reabsorption [12]. Generally known; higher insulin and HOMA-IR are detected in those with low phosphate levels [13,14]. The first study that investigated the relationship between FGF-23 level and insulin was published in 2012 [15]. In this study of 68 adolescents with obesity, it was found a negative correlation between FGF-23 level and fasting insulin level. All these results suggest that FGF-23 may be a contributing factor to insulin sensitivity. But the relationship between FGF-23 level and IR in patients with PCOS had not been previously evaluated. When our patients were grouped as those with and without IR, the FGF-23 level was statistically significantly lower in the IR group.

FGF-23 is a factor that affects circulating phosphate and vitamin D levels. Recently, this molecule was shown to play a role in many other metabolic processes besides its key role in the pathogenesis of calcium-phosphorus disorders. The contribution of FGF-23 to metabolic syndrome and its circulatory system-related complications is investigated. The “molecular similarity” hypothesis has been proposed to explain the role of FGF-23 in the regulation of insulin sensitivity. FGF-23 is 22%–24% similar to FGF-21, which was shown to have a role in glucose and lipid metabolism. FGF-21 improves hyperglycemia, dyslipidemia, and obesity, providing a therapeutic effect on metabolic diseases [16]. In a study investigating FGF-21 levels in patients with PCOS; FGF-21 levels were similar in women with PCOS compared with those of age- and BMI- matched controls [17].

Multiple morbidities are associated with PCOS, including infertility, metabolic syndrome, obesity, impaired glucose tolerance, IR, type 2 diabetes mellitus, cardiovascular risk, depression, obstructive sleep apnea, endometrial cancer, and nonalcoholic fatty liver disease/ nonalcoholic steatohepatitis. IR and hyperinsulinemia were shown to have a protective effect against bone mineral loss in PCOS [18], however, the mechanism by which this effect occurs has not been fully revealed. However, in some studies, lower bone mineral density was detected in PCOS patients than healthy controls independently of body mass index [19]. Studies comparing bone mineral density or bone metabolism and the risk of bone fractures in women with PCOS have controversial results. In another study with large participation; patients with PCOS had a higher incidence of any fractures compared with non-PCOS group and a greater risk of any fractures, osteoporotic fractures, spine fractures and forearm fractures [20]. High glucose environment probably induces osteoblast apoptosis, resulting in decreased bone mineral density and increased fracture risk.

Conflicting results were obtained in studies researching the relationship between FGF-23 and bone turnover. Some investigators showed that FGF-23 inhibits bone mineralization and osteoblastic activity [21,22]. Contrarily, some studies showed that increased FGF-23 levels increase osteoblastic activity, bone healing and fusion [23-25]. The largest study that evaluates FGF-23 level and BMD was conducted in Sweden [26]. Wherein, 3014 Swedish male patients aged 69–80 years were evaluated, which revealed a weak correlation between the FGF-23 levels and BMD. However, increased FGF-23 level was shown to be affected by body weight and when this factor is corrected, FGF-23 does not play an important role in the hormonal control of BMD. Our study revealed that there is no significant relationship between FGF-23 levels and BMD in patients with PCOS. In addition, the FGF-23 level was lower in the PCOS group compared to the control group, probably because the excess of estrogen, which is not met with progesterone, causes a decrease in the FGF-23 level because anovulation is common in these patients. This finding is supported by increased FGF-23 levels in studies in estrogen-deficient individuals [27,28]. Consistent with this, in our study, FGF-23 was found to be lower in patients with amenorrheic PCOS.

When the patients in the PCOS group were grouped as those with and without hyperandrogenemia, the FGF-23 level did not make a statistically significant difference between these two groups. The positive effects of androgens on bones are thought to be invalid in patients with PCOS, and this is probably due to some factors in the pathogenesis that are unknown. In a recent study investigating the association between endogenous sex hormones and FGF-23; unlike our study, among 2,868 postmenopausal women, 1 SD increment in free testesteron was associated with 3% higher FGF-23 [29].

In conclusion, our study found lower FGF-23 levels in patients with PCOS. In addition, the low level of FGF-23 in the PCOS group with IR suggests that this marker may also be associated with the complications of PCOS,

but to clarify this hypothesis, this marker needs to be investigated. It would be helpful to do further researches and run well-designed clinical trials in a higher number of patients with PCOS who have complications.

Ethics committee Approval: This study was approved by the ethics committee of Cumhuriyet University Faculty of Medicine with the decision dated 05.03.2013 and numbered 2013-03/25.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author contributions: Concept- E.Ç., F.K.; Design- F.K, E.Ç; supervision- S.Ç., F.K.; resource- E.Ç.; materials- E.Ç., F.K.; Data collection and/ or procesing- E.Ç., S.Ç.; Analysis and/or interperation- S.Ç., E.Ç. Literature Search- S.Ç., E.Ç.; Writing- E.Ç., S.Ç.; Critical Reviews- F.K., E.Ç.

Conflict of interest: No conflict of interest was declared by the authors.

Data availability statement: The laboratory data generated in this study is available from the corresponding author on reasonable request.

Funding: This study was supported by the Unit of the Cumhuriyet University Scientific Research Projects (CÜBAP) with T574 numbered project.

References

1. Ganie MA, Vasudevan V, Wani IA, Baba MS, Arif T, Rashid A. Epidemiology, pathogenesis, genetics & management of polycystic ovary syndrome in India. Indian J. Med Res. 2019; 150(4): 333–344.

2. Ibanez L, Oberfield SE, Witchel SF,Auchus RJ, Chang RJ, Codner E, Dabadghao P, Darendeliler F, Elbarbary N, Gambineri A, Rudaz CG, Hoeger KM, Bermejo AL, Ong K, Pena AS, Reinehr T, Santoro N, Sempere MT, Tao R, Yildiz BO, Alkhayyat H, Deeb A, Joel D, Horikawa R, Zegher F, Lee P. An International Consortium Update: Pathophysiology, Diagnosis, and Treatment of Polycystic Ovarian Syndrome in Adolescence. Horm. Res. Paediatr. 2017; 88(6): 371–395

3. Li Y, Chen C, Ma Y, Xiao J, Luo G, Li Y, Wu D. Multi-system reproductive metabolic disorder: Significance for the pathogenesis and therapy of polycystic ovary syndrome (PCOS). Life Sci. 2019;228:167–175.

4. Zeng X, Xie Y-J, Liu Y-T, Long S-L, Mo Z-C. Polycystic ovarian syndrome: Correlation between hyperandrogenism, insulin resistance and obesity. Clin. Chim. Acta. 2020; 502: 214–221.

5. Zhang C, Hu J, Wang W, Sun Y, Sun K. HMGB1-induced aberrant autophagy contributes to insulin resistance in granulosa cells in PCOS. FASEB J. 2020; 34(7): 9563–9574.

6. Toosy S, Sodi R, Pappachan JM. Lean polycystic ovary syndrome (PCOS): an evidence-based practical approach. J Diabetes Metab Disord. 2018; 17(2):277–285.

7. Liu S, Guo R, Simpson LG, Xiao ZS, Burnham CE, Quarles LD. Regulation of fibroblastic growth factor 23 expression but not degradation by PHEX. J Biol Chem. 2003; 278 (39): 37419-26.

8. Miyamoto K, Ito M, Kuwahata M, Kato S, Segawa H. Inhibition of intestinal sodium-dependent inorganic phosphate transport by fibroblast growth factor 23. Ther Apher Dial. 2005; 9(4):331-5.

9. Danziger J. The bone-renal axis in early chronic kidney disease: an emerging paradigm. Nephrol Dial Transplant. 2008; 23(9):2733-37.

10. Lu Y, Feng JQ. FGF23 in skeletal modeling and remodeling. Curr Osteoporos Rep. 2011; 9(2):103-8.

11. Martínez-García MA, Moncayo S, Insenser M, Álvarez-Blasco F, Luque-Ramírez, M, Escobar-Morreale H. F. Metabolic Cytokines at Fasting and During Macronutrient Challenges: Influence of Obesity, Female Androgen Excess and Sex. Nutrients. 2019; 11(11): 2566.

12. Murer H, Hernando N, Forster I, Biber J. Proximal tubular phosphate reabsorption: Molecular mechanisms. Physiological Reviews. 2000; 80(4): 1373–1409.

13. Abuduli M, Ohminami H, Otani T, Kubo H, Ueda H, Kawai Y, Masuda M, Yamanaka-Okumura H, Sakaue H, Yamamoto H, Yamamoto H, Takeda E, Taketani Y. Effects of dietary phosphate on glucose and lipid metabolism. Am. J. Physiol. Endocrinol. Metab. 2016; 310(7): E526-38.

14. Akter S, Eguchi M, Kochi T, Kabe I, Nanri A, Mizoue T. Association of Serum Calcium and Phosphate Concentrations with Glucose Metabolism Markers: The Furukawa Nutrition and Health Study. Nutrients. 2020; 12(8): 2344.

15. Wojcik M, Dolezal-Oltarzewska K, Janus D, Drozdz D, Sztefko K, Starzyk JB. FGF23 contributes to insulin sensitivity in obese adolescents — preliminary results. Clinical Endocrinology. 2012; 77(4): 537–40.

16. Geng L, Lam KSL, Xu A. The therapeutic potential of FGF21 in metabolic diseases: from bench to clinic. *Nat Rev Endocrinol.* 2020; 16(11) :654–667.

17. Sahin SB, Ayaz T, Cure MC, Sezgin H, Ural UM, Balik G, Sahin FK. Fibroblast growth factor 21 and its relation to metabolic parameters in women with polycystic ovary syndrome. ScandJ Clin Lab Invest. 2014; 74(6): 465–469

18. Yüksel O, Dökmetaş HS, Topcu S, Erselcan T, Sencan M. Relationship between bone mineral density and insulin resistance in polycystic ovary syndrome. J Bone Miner Metab. 2001; 19(4):257-62

19. Mørch NF, Aziz M, Svendsen PF. Bone mass density in lean and overweight women with polycystic ovary syndrome. ScandJ Clin Lab Invest. 2022; 82(3): 210–217

20. Yang HY, Lee HS, Huang WT, Chen MJ, Chen SC, Hsu YH. Increased risk of fractures in patients with polycystic ovary syndrome: a nationwide population-based retrospective cohort study. J Bone Miner Metab. 2018; 36(6), 741–748.

21. Zhang R, LuY, YeL, Yuan B, YuS, Qin C, Xie Y, Gao T, Drezner MK, Bonewald LF, Feng JQ. Unique roles of phosphorus in endochondral bone formation and

osteocyte maturation. J Bone miner Res. 2011; 26(5): 1047-56.
22. Wang H, Yoshiko Y, Yamamoto R, Minamizaki T, Kozai K, Tanne K, Aubin JE, Maeda N. Overexpression of fibroblast growth factor 23 suppresses osteoblast differention and matrix mineralization in vitro. J. Bone Miner Res.2008; 23(6):939·48.
23. Kawata T, Imanishi Y, Kobayashi K, Miki T, Arnold A, Inaba M, Nishizawa Y. Parathyroid hormone regulates fibroblast growth factor-23 in a mouse model of primary hyperparathyroidism. J Am Soc Nephrol. 2007; 18(10): 2683-8.
24. Bellido T, Ali AA, Gubrij I, Plotkin LI, Fu Q, O'Brien CA, Manolagas SC, Jilka RL. Chronic elevation of parathyroid hormone in mice reduces expression of sclerostin by osteocytes: a novel mechanism for hormonal control of osteoblastogenesis. Endocrinology. 2005; 146(11):4577-83.
25. Goobel S, Lienau J, Rammoser U, Seefried L, Wintgens KF, Seufert J, Duda G, Jakob F, Ebert R. FGF23 is a putative marker for bone healing and regeneration. J Orthop Res.2009; 27(9) :1141-46.
26. Westerberg PA, Tivesten Å, Karlsson MK, Mellström D, Orwoll E, Ohlsson C, Larsson TE, Linde T, Ljunggren Ö. Fibroblast growth factor 23, mineral metabolism and mortality among elderly men (Swedish MrOs) BMC Nephrol. 2013; 14:85.
27. Celik E, Guzel S, Abalı R, Guzelant AY, Guzel EC, Kucukyalcin V. The relationship between fibroblast growth factor 23 and osteoporosis in postmenapousal women. Minerva Med.2013; 104(5):497-504.
28. Ix JH, Chonchol M, Laughlin GA, Shlipak MG, Whooley MA. Relation of sex and estrogen therapy to serum fibroblast growth factor 23, serum phosphorus, and urine phosphorus: the Heart and Soul Study. Am J Kidney Dis. 2011; 58(5):737-45.
29. Ogunmoroti O, Osibogun O, Zhao D, Mehta RC, Ouyang P, Lutsey PL, Robinson-Cohen C, Michos E D. Associations between endogenous sex hormones and FGF-23 among women and men in the Multi-Ethnic Study of Atherosclerosis. PloS one. 2022; 17(5): e0268759.