

# Correlation between HbA1c and fibrocystic breast disease among polycystic ovary syndrome

## Polikistik over sendrom'nda HbA1c ve fibrokistik meme hastalığı korelasyonu

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### SUMMARY




**Objective:** The aim of this study is to investigate whether Hemoglobin A1c (HbA1c) levels in polycystic ovary syndrome (PCOS) can predict the risk of fibrocystic breast disease in women applied to the Gynecology&Obstetrics outpatient clinic.

**Method:** This retrospective study was conducted from January 2018 to February 2020 on 269 women. The subjects were divided into two groups as PCOS group (Group 1) and control group (Group 2), respectively.

**Results:** The mean age of all participants was  $33.13 \pm 1.93$  years. Most of the subjects had normal Body mass index (BMI) ( $35.3\%$ ;  $25.7 \pm 1.44$ ).  $50.6\%$  had the risk of fibrocystic breast disease. The mean age of menarche was  $11.36 \pm 0.97$ , and the mean level of HbA1c was  $5.57 \pm 0.37$ . FSH ( $p < 0.001$ ), LH ( $p < 0.001$ ), HbA1c ( $p = 0.001$ ), fasting glucose ( $p = 0.001$ ) and AMH ( $p = 0.001$ ) were significantly different between the two groups. Prevalence of fibrocystic breast disease and smoking ( $p=0.03$  and  $0.02$ , respectively) were significantly different at HbA1c levels among the control group. There was a statistically significant difference ( $p=0.04$  and  $0.04$ ) between the fibrocystic breast disease and HbA1c levels i.e.  $5.7 \leq \text{HbA1c} \leq 6$  and  $\text{HbA1c} > 6$  in the control group.

**Conclusions:** It was concluded that HbA1c cannot be used for assessment of the fibrocystic breast disease in the PCOS women but can predict the fibrocystic breast disease in healthy women. There may be a need for additional diagnostic tests for the PCOS women to assess the fibrocystic breast disease for early treatment.

**Keywords:** Fibrocystic breast disease, HbA1c, polycystic ovary syndrome

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### ÖZET

**Amaç:** Bu çalışmanın amacı; kadın doğum polikliniğine Polikistik over sendromu (PKOS) ile başvuran kadınlarda, Hemoglobin A1c (HbA1c) düzeylerinin, fibrokistik meme hastalığı riskini öngörüp öngöremeyeceğini araştırmaktır.

**Yöntem:** Bu retrospektif çalışma, Ocak 2018-Şubat 2020 tarihleri arasında polikliniğe başvuran 269 kadın üzerinde gerçekleştirilmiştir. Katılımcılar, sırayla, PCOS grubu (Grup 1) ve kontrol grubu (Grup 2) olarak iki gruba ayrılmıştır.

**Bulgular:** Tüm katılımcıların yaş ortalaması  $33,13 \pm 1,93$  olup, katılımcıların çoğunun vücut kitle indeksi (VKİ) normal düzeydedir ( $\% 35,3$ ;  $25,7 \pm 1,44$ ). Katılımcıların  $\%50,6$ 'sı için fibrokistik meme hastalığı riski söz konusudur. Katılımcıların ortalama menarş yaşı  $11,36 \pm 0,97$ , ortalama HbA1c seviyesi ise  $5,57 \pm 0,37$ 'dir. FSH ( $p < 0,001$ ), LH ( $p < 0,001$ ), HbA1c ( $p = 0,001$ ), açlık glikozu ( $p = 0,001$ ) ve AMH ( $p = 0,001$ ) düzeylerinin iki grup arasında anlamlı farklılık

gösterdiği görülmüştür. Fibrokistik meme hastalığı ve sigara içme prevalansı (sırasıyla  $p = 0.03$  ve  $0.02$ ), kontrol grubu arasında HbA1c düzeyleri bakımından anlamlı farklılık barındırmaktadır. Kontrol grubunda fibrokistik meme hastalığı ile HbA1c düzeyleri, yani  $5.7 \leq \text{HbA1c} \leq 6$  ve  $\text{HbA1c} > 6$  arasında, istatistiksel olarak anlamlı bir fark saptanmıştır ( $p = 0.04$  ve  $0.04$ ).

**Sonuç:** PKOS hastası kadınlarında fibrokistik meme hastalığının değerlendirilmesinde HbA1c düzeyinin kullanılamayacağı, ancak HbA1c'nin sağlıklı kadınlarda fibrokistik meme hastalığını tahmin edebileceği sonucuna varılmıştır. PKOS hastalarında, fibrokistik meme hastalığını değerlendirmek üzere erken tanı ve tedavide ek tanı testlerine ihtiyaç duyulmaktadır.

**Anahtar sözcükler:** Fibrokistik meme hastalığı, HbA1c, polikistik over sendromu.

## INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disease affects women of reproductive age and is one of the main causes of reduced fertility among women, as seen in 50% of women at the fertility age. The main consequences of PCOS are the psychological and physical problems in women, significantly reducing the quality of life<sup>1</sup>. The main clinical manifestations of this syndrome are infertility, hirsutism, and metabolic problems such as glucose intolerance. About 10% of these patients have glucose intolerance. Besides, PCOS patients suffer from serious side effects such as breast cancers, hyperlipidemia, cardiovascular illness, hypertension, diabetes, and high risk of endometrial cancer<sup>2</sup>. It is not clear what its main cause is but some researchers found diabetes and heredity factors as effective factors<sup>3</sup>. Other changes include increased testosterone, dehydroepiandrosterone sulphate (DHEASO<sub>4</sub>) and Luteinizing hormone (LH) levels<sup>4</sup>. In addition, prolactin, insulin, and hemoglobin A1C (HbA1c) levels are affected and insulin resistance is seen in these patients<sup>5</sup>.

Hb is one of the proteins inside red globules, which carries oxygen to the blood. Like all other proteins in the body, Hb is combined with sugars including glucose. Until the red globule is alive, this combination is preserved (for about 120 days). Hb has different types naturally comprising 95-97% of A1c. Connecting sugar to this hemoglobin leads to HbA1c or glycosylated hemoglobin. In Hb A1C, glucose is connected to the end N-terminal amino acid valine of the beta chain of hemoglobin A<sup>6</sup>. This process includes the HbA1c Test.

Fibrocystic changes are the most common benign lesions of the breast. These changes usually affect women between the ages of 20 and 50. Fibrocystic breast disease is associated with lumps in the breasts and cyclical breast pain. About 70 % of women at reproductive age regularly experience cyclic breast pain, and 10-30% of them suffer from pain which is severe enough to disrupt normal activities<sup>7</sup>. Fibrocystic breast disease causes to

increase the risk of breast cancer. Increasing changes in the tissue will increase the risk which will be doubled due to proliferative changes and will increase fourfold due to atypical hyperplasia<sup>8</sup>.

The fibrocystic breast disease is clinically characterized by tenderness or axillary pain in response to the progress of nodularity, macrocysts, fibrocystic plaques, and fibrocystic lumps. With increasing premenopausal age, the disease will progress and will be more prevalent among the women at the age of 40<sup>9</sup>.

In this study, we aimed to investigate if increased HbA1c levels in PCOS patients can predict the risk of fibrocystic breast disease in the women aged between 30 and 40 years.

## MATERIAL AND METHODS

This retrospective study was conducted in Adana City Hospital (Adana Numune Training and Research Hospital) from January 2018 to February 2020 on 269 women diagnosed with Irregular Menstruation, and Polycystic Ovary Syndrome, with the mean age of  $33.13 \pm 1.93$ , who applied to the Gynecology and Obstetrics outpatient clinic. The patients files with PCOS diagnosis were evaluated based on the Rotterdam 2003 diagnostic criteria. HbA1c level was studied in the electronic files of PCOS patients and three patients who underwent breast ultrasound with various indications were investigated. The subjects were divided into two groups as PCOS (Group 1) and control group (Group 2). The women who were diagnosed with PCOS at the ages of 18-45, non-smokers, had no more systemic disease, showed HbA1c result and breast ultrasonography and fibrocystic breast were included in the study. The pregnant women, the smokers and those with continuing lactation and those who had systemic disease were excluded from the study.

This study was approved by the university /local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki

Declaration and its later amendments or comparable ethical standards. The study was carried out with the permission of Research Ethics Committee of Adana City Training Hospital (Permission granted /CAAE number: 2020/17.06, Decision no: 941).

### Statistical methods

SPSS statistical software for Windows (Statistical Package for Social Sciences, version 16.0, SPSS Inc. Chicago, Illinois, USA) was used to evaluate the study results. Descriptive statistics results were given as mean  $\pm$  standard deviation or median (minimum-maximum) for numerical variables and number and / or percentage of patients for categorical variables. All continuous data were expressed as mean  $\pm$  standard deviation. Shapiro-Wilk test indicated the assumption of normality was not met for the quantitative variables. Then, non-normally distributed variables were compared between two and more than two groups using the Mann-Whitney and Kruskal-Wallis tests. A Chi-square test was used to compare qualitative variables between the groups. A p-value below 0.05 was considered statistically significant.

Logistic regression was used for assessing the association between the fibrocystic breast disease and HbA1c levels.

### RESULTS

The mean age of all participants was  $33.13 \pm 1.93$  ranged from 30 to 40 years. Most of the subjects were characterized by normal BMI (35.3%;  $25.7 \pm 1.44$ ). Among all the participants, 50.6 % were found to have the risk of fibrocystic breast disease, 7.8 % had a family history, 34.9% were smokers. The mean age of menarche was  $11.36 \pm 0.97$ , and the mean of HbA1c was  $5.57 \pm 0.37$ .

Table 1 shows the detailed comparison of clinical, biochemical and ultrasonographic parameters in healthy and PCOS groups. No statistical significance was observed between the control and PCOS group in Age ( $P = 0.55$ ), BMI ( $P = 0.71$ ), Mean age at menarche ( $P = 0.35$ ), Fibrocystic breast disease ( $P = 0.17$ ), and smoking status ( $P = 0.66$ ). However, FSH( $P < 0.001$ ), LH ( $P < 0.001$ ), HbA1c ( $P = 0.001$ ), fasting glucose ( $P = 0.001$ ) and AMH ( $P = 0.001$ ) were significantly different between the two groups (Table 1).

**Table 1:** Clinical, biochemical and ultrasonographic parameters according to HbA1c level in healthy and PCOS group

		PCOS GROUP (n=102)	CONTROL GROUP (n=167)	P value
FSH		$5.76 \pm 1.86$	$7.77 \pm 0.65$	$< 0.001^*$
LH		$12.25 \pm 1.86$	$7.75 \pm 0.66$	$< 0.001^*$
E2		$43.42 \pm 5.48$	$42.89 \pm 5.47$	0.54
Age(years)		$33.02 \pm 1.99$	$33.20 \pm 1.90$	0.55
HbA1c (%)		$5.78 \pm 0.25$	$5.44 \pm 0.37$	$< 0.001^*$
BMI (kg/m <sup>2</sup> )		$25.74 \pm 1.45$	$25.67 \pm 1.44$	0.71
Fasting glucose (mmol/L)		$90.62 \pm 4.03$	$85.32 \pm 7.36$	$< 0.001^*$
Mean age at menarche (y)		$11.41 \pm 0.99$	$11.32 \pm 0.96$	0.35
AMH		$5.24 \pm 0.81$	$1.86 \pm 0.33$	$< 0.001^*$
Fibrocystic breast disease(n,%)	yes	(57, 55.9 % )	(79, 47.3 % )	0.17
	no	(45, 44.1 % )	(88, 52.7 % )	
Current smokers (n,%)	yes	(34, 33.3 % )	(60, 35.9 % )	0.66
	no	(68, 66.7 % )	(107, 64.1 % )	

Table 2 shows the clinical, biochemical and ultrasonographic parameters in terms of HbA1c levels in women with PCOS. Age ( $p=0.71$ ), HbA1c ( $p < 0.001$ ), BMI ( $p=0.46$ ), Mean age at menarche ( $p=0.65$ ), Fibrocystic breast disease ( $p=0.35$ ) and smoking ( $p=0.24$ ) among the women with PCOS were not significantly different at three levels of HbA1c  $<5.7$ ,  $5.7 \leq \text{HbA1c} \leq 6$  and  $\text{HbA1c} >6$ .

Table 3 shows the clinical, biochemical and ultrasonographic parameters according to HbA1c levels in the control group. In healthy women, the

prevalence rates of fibrocystic breast disease and smoking ( $p=0.03$  and  $0.02$ , respectively) were significantly different at HbA1c levels. The higher prevalence of fibrocystic breast disease, the higher level of HbA1c.

Table 4 shows logistic regression for assessing the association between fibrocystic breast disease and HbA1c levels. There is a statistically significant difference ( $p=0.04$  and  $0.04$ ) between the fibrocystic breast disease and HbA1c levels i.e.  $5.7 \leq \text{HbA1c} \leq 6$  and  $\text{HbA1c} >6$  in the control group.

**Table 2:** Clinical, biochemical and ultrasonographic parameters according to HbA1c level in women with PCOS

	HbA1c <5.7 (n=35)	5.7 ≤ HbA1c ≤6 (n=55)	HbA1c >6 (n=12)	P value
Age(years)	32.94 ± 2.40	33.11 ± 1.81	32.83 ± 1.53	0.71
HbA1c	5.50 ± 0.11 <sup>ac</sup>	5.86 ± 0.06 <sup>ab</sup>	6.24 ± 0.13 <sup>bc</sup>	< 0.001*
BMI (kg/m <sup>2</sup> )	25.54 ± 1.31	25.78 ± 1.50	26.17 ± 1.59	0.46
Mean age at menarche (y)	11.57 ± 1.19	11.33 ± 0.90	11.33 ± 0.65	0.65
Fibrocystic breast disease(n,%)	yes	(18, 51.4 %)	(30, 54.5 %)	0.35
	no	(17, 48.6 %)	(25, 45.5%)	
Current smokers (n, %)	yes	(8, 22.9 %)	(21, 38.2 %)	0.24
	no	(27, 77.1 %)	(34, 61.8 %)	

a: Mean difference between the first and second categories has been significant.  
b: Mean difference between the second and third categories has been significant.  
c: Mean difference between the first and third categories has been significant.

**Table 3:** Clinical, biochemical and ultrasonographic parameters according to HbA1c levels in the control group

	HbA1c <5.7 (n=107)	5.7 ≤ HbA1c ≤6 (n=49)	HbA1c >6 (n=11)	P value
Age(years)	33.30 ± 1.94	33.12 ± 1.68	32.54 ± 2.42	0.26
HbA1c	5.22 ± 0.23 <sup>ac</sup>	5.77 ± 0.07 <sup>a</sup>	6.21 ± 0.07 <sup>c</sup>	< 0.001*
BMI (kg/m <sup>2</sup> )	25.83 ± 1.48	25.29 ± 1.19	25.82 ± 1.89	0.19
Mean age at menarche (y)	11.28 ± 0.91	11.43 ± 1.08	11.27 ± 0.90	0.68
Fibrocystic breast disease(n,%)	yes	(43, 40.2 %)	(8, 72.7 %)	0.03*
	no	(64, 59.8 %)	(21, 42.9 %)	
Current smokers (n, %)	yes	(41, 38.3 %)	(0, 0%)	0.02*
	no	(66, 61.7 %)	(11, 100 %)	

a: Mean difference between the first and second categories has been significant.  
c: Mean difference between the first and third categories has been significant.

**Table 4:** The results of logistic regression for assessing the association between the Fibrocystic breast disease and HbA1c levels

		PCOS group			Control group		
		Fibrocystic breast disease (Yes vs No)			Fibrocystic breast disease (Yes vs No)		
		OR	95% C.I.	P-value	OR	95% C.I.	P-value
Model 1	HbA1c <5.7	-	-	-	-	-	-
	5.7 ≤ HbA1c ≤6	1.11	0.47 – 2.61	0.81	1.96	0.97 – 3.95	0.06
	HbA1c >6	2.87	0.66 – 12.52	0.15	3.60	0.86 – 15.12	0.07
Model 2	HbA1c <5.7	-	-	-	-	-	-
	5.7 ≤ HbA1c ≤6	0.99	0.41 – 2.41	0.9	<b>2.13</b>	<b>1.03 – 4.40</b>	<b>0.04</b>
	HbA1c >6	2.47	0.55 – 11.07	0.23	<b>4.55</b>	<b>1.05 – 19.64</b>	<b>0.04</b>

Model 1: adjusted for age; Model 2: adjusted for age, BMI, age at menarche, smoking status.

## DISCUSSION

The present study showed no statistically significant difference between the control and PCOS group in age, BMI, mean age at menarche, fibrocystic breast disease, and smoking status. However, FSH, LH, HbA1c, fasting glucose, and

AMH were significantly different between the two groups. In other words, LH, HbA1c, fasting glucose (mmol/L), and AMH were significantly higher in the PCOS group than in the control group but FSH was significantly lower in the PCOS group than in the control group. There was no statistically significant difference at three levels of HbA1c

<5.7,  $5.7 \leq \text{HbA1c} \leq 6$ , and  $\text{HbA1c} > 6$  in terms of Age, HbA1c, BMI, mean age at menarche, fibrocystic breast disease, and smoking among the women with PCOS.

HbA1c levels did not significantly affect fibrocystic breast disease among the women with PCOS while there was a statistically significant difference between the fibrocystic breast disease and HbA1c levels in the control group. The higher prevalence of fibrocystic breast disease, the higher level of HbA1c in the healthy group. In this study, the PCOS group did not show a significant difference between the fibrocystic breast disease and HbA1c levels while the healthy control group showed a significant difference between fibrocystic breast disease and HbA1c levels.

PCOS which is the most common endocrine disorder among the women at reproductive age has clinical symptoms such as hyperandrogenism, anovulatory infertility, and is associated with obesity and insulin resistance<sup>10</sup>. Recent studies suggested a significant relationship between PCOS and fibrocystic breast disease.

Our study results are not in line with the results of the study by<sup>11</sup>, who found a significant association between PCO and benign pathology and Gumus et al.<sup>12</sup> who found a statistically significant association between a PCOS and fibrocystic breast disease which showed a clear correlation but consistent with results of the study by Soran et al.<sup>13</sup> who suggested that both the experimental and control groups showed similar rates of hyperplasia, discharge, redness, pain, calcification, fibroadenoma, and fibrocystic breast disease and Sarac et al.<sup>14</sup> who found no different characteristics of breast parancime pattern between the PCOS and control groups, indicating no increase in the breast cystic disease does due to PCOS.

Krishnamoorthy et al.<sup>15</sup> found no variations in FSH and LH between the healthy group and the women with benign breast disease, which does not support our study results that FSH and LH were significantly different between the two groups.

Amin<sup>6</sup> found a significant relationship between age and HbA1c levels and a significant relationship between fasting blood glucose and HbA1c levels while our study showed no significant difference between age and HbA1c levels but found that fasting glucose was significantly higher in the PCOS group than in the control group.

A study by Golland et al.<sup>5</sup> found that patients with PCOS had higher levels of HbA1c levels which was not associated with glucose tolerance disorder, which is in line with our study results that found

HbA1c to be significantly higher in the PCOS group than in the control group.

Our study results are not consistent with the results of a study by Silfen et al.<sup>16</sup> who found that HbA1c levels and fasting glucose were similar between the obese PCOS and control groups and that none of them had impaired fasting glucose or diabetes.

Our results are also consistent with the studies by Dunaif<sup>17</sup> who found that an inherent component of PCOS as reducing insulin sensitivity due to defective post-receptor binding in the insulin signaling pathways independent of obesity and González et al.<sup>18</sup> who found PCOS to be associated with high glycooxidative stress.

Our study results are not in line with the results of studies by Pasquali et al.<sup>19</sup> who reported that obese girls were more exposed to PCOS, insulin resistance, and metabolic syndrome, Randeva et al.<sup>20</sup> who found that the women with PCOS were at a higher risk of obesity and Mauvais et al.<sup>21</sup> and Pfeifer et al.<sup>22</sup> who showed obesity to exacerbate impaired glucose tolerance and insulin resistance in women with PCOS.

Renuka et al.<sup>23</sup> found that patients with PCOS had significantly higher levels of HbA1c than the control group had, which is consistent with our study results.

Our study results are not in line with the study results by Lin et al.<sup>25</sup> who found no association between higher HbA1c levels and high risk of breast cancer and also no significant association with HbA1c levels based on lymph node metastasis and tumor size but consistent with a study which found a high risk of breast cancer with increased fasting glucose levels<sup>24</sup> and Lin et al.<sup>25</sup> who found higher HbA1c concentrations not to increase risk of breast cancer among healthy women. Our study found that the higher prevalence of fibrocystic breast disease, the higher level of HbA1c in the healthy group.

## CONCLUSION

In the present study, it is concluded that the PCOS group did not show a significant difference between the fibrocystic breast disease and HbA1c levels while the healthy control group showed a significant difference between the fibrocystic breast disease and HbA1c levels. The present study shows that HbA1c cannot be used for assessment of the fibrocystic breast disease in the PCOS women but can predict the fibrocystic breast disease in healthy women. There may be a need for additional diagnostic tests for the PCOS women to assess the fibrocystic breast disease for early treatment.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Research Ethics Committee of Adana City Training Hospital (Permission granted /CAAE number: 2020/17.06, Decision no: 941).

**Informed Consent:** Written informed consent was obtained from all participants who participated in this study.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

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**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version

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