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Correlation Between Serum Interleukins levels with Anthropometric Data and Lipid Profiles in Obese Iraqi Women With Polycystic Ovary Syndrome

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Abstract

This study was performed to assess the correlation of serum interleukins (ILs) levels with anthropometric data and lipid profile status in blood samples obtained from 100 Iraqi obese women with polycystic ovary syndrome PCOS. Obese non PCOS healthy women (n=75) matching in age (19-38 years) and body mass index(29.9-33.4kg/m^2) served as a control group. The samples were collected from Kamal Al-Samurai Teaching hospital during the period of December 2017- June 2018.ELISA kits were used to measure serum levels of IL-6,IL-10,IL-18, IL-29,IL-33,tumor necrotic factor (TNF-α),high sensitive C-reactive protein (hsCRP), insulin, total testosterone, and sex hormone binding globulin(SHBG).The biochemical measurements of blood glucose and lipid profile were performed by conventional colorimetric methods. The results demonstrated significant differences($P < 0.01$) in serum levels of all interleukins and lipid profile parameters in obese PCOS in comparison with obese on PCOS control women.In addition, PCOS women had higher insulin and FAI levels in comparison to non PCOS women. The findings suggest that androgen excess, indicated by high free androgen index (FAI),might serve as an indicator of a prediabetic status, as it might promote insulin resistance and β-cell dysfunction in PCOS women. Circulatory interleukin levels in obese PCOS women may act on the development of insulin resistance and androgen oversupply in PCOS,suggesting that high serum ILs levels were related to insulin resistance (IR) and androgen excess but not to body mass index. A high IL level is not an elemental characteristic of PCOS, but it may act in promoting IR and hyperandrogenism of PCOS.

Keywords: IL, polycystic ovary syndrome, Obesity

العلاقة بين المستويات المصلية للحركيات الخلوية وبيانات الانثروبومترك ونمط الدهون في النساء العراقيات البدينات المصابات بمتلازمة تعدد الأكياس المبيضية

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الخلاصة

تمت هذه الدراسة لتقييم العلاقة بين مستويات الحركيات الخلوية و بيانات الانثروبومترك ونمط الدهنيات في مائة عينة من دم النساءالبدينات المصابات بمتلازمة تعدد الأكياس المبيضية متطابقين من حيث العمر ومؤشر كتلة الجسم مع خمسة وسبعون عينة من النساء البدينات السليمات (السيطرة)والتي جمعت من

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مستشفى كمال السامرائي التعليمي للفترة من كانون الأول 2017 والى حزيران 2018. تم قياس جميع مستويات الحركيات الخلوية33،29،18،10،6وعامل النخر الورمي, بروتين ج عالي الحساسية وهرمون الأنسولين, هرمون التستيرون الكلي,الهرمون الجنسي الرابط للكلوبلين باستخدام تقنية الاليزا,بالإضافة إلى القياسات الكيميائية لمستوى سكر الكلوكوز و نمط الدهنيات بواسطة الطرق التقليدية الطيفية . أوضحت النتائج وجود تغيرات معنوية ذات مدلول إحصائي في المستويات المصلية لجميع الحركيات الخلوية والدهنيات عند مرضى

متلازمة تعدد الأكياس المبيضية مقارنة بالنساء السليمات ,إضافة إلى أن مرضى تكيس المبايض المتعدد لديهم مستويات عالية من الأنسولين وقيم معامل الاندروجين الحر بالمقارنة مع النساء السليمات. لذا فان هذه البيانات تقترح بان وفرة الاندروجين المؤكدة بقيم معامل الاندروجين الحر ربما تعتبر كدليل مبكر للكشف عن حالة ماقبل السكري والتي تزيد من مقاومة هرمون الأنسولين وخلل في وظيفة خلايا بيتا في مرضى تكيس المبايض المتعدد. أن مستويات الحركيات الخلوية في الدورة الدموية لدى نساء متلازمة تكيس المبايض البدينات قد تعمل على تطور مقاومة الأنسولين ووفرة, الاندروجين لديهم والتي تشير إلى أن مستويات الحركيات الخلوية عالية في المصل كانت مرتبطة بمقاومة الأنسولين وزيادة الأندروجين ولكن ليس لمؤشر كتلة الجسم إي تأثير لذلك ، لذا فإن مستويات الحركيات الخلوية المرتفعة ليست من الخصائص الأولية لمتلازمة تكيس المبايض المتعدد ، ولكنها قد تعمل في تعزيز مقاومة الأنسولين وفرط الأندر وجين في متلازمة تكيس المبايض.

Introduction

Polycystic ovarian syndrome(PCOS) is considered as a heterogeneous accumulation of signs and symptoms that construct a spectrum of a common disorder of premenopausal women distinguished by clinical and hormonal features[1, 2].The pathophysiology of PCOS seems to be multifactorial and polygenic, with the major characteristics including menstrual cycle disarrangement, excess in androgen secretion , and obesity[3]. PCOS has significant and numerous clinical issues, including endocrine, reproductive, and metabolic disorders such as excess androgen secretion and adiposity. Abdominal obesity is an unconstrained influence aggravated by PCOS endocrine disorders sucha s those in the subcutaneous abdominal adipose tissues and the liver tissue that lead to extragonadal aromatization[4].

Ample evidence considered that PCOS is a proinflammatory disorder associated with chronic low-grade inflammation persistence, with the presence of elevated levels of several inflammatory cytokines correlated with insulin resistance [5]. Obesity and diabetes mellitus were also found to be associated with the PCOS [6]. Elevated levels of inflammation moderators, such as adipokines [7]and cytokines [8,9], were found in the serum of PCOS patients. Recently,Interleukin-29 was reported to be a key proinflammatory cytokine that possesses an important role in the development and metabolism of PCOS, but with a yet unknown mechanism of action[10]. Therefore, investigating the function of IL-29 in PCOS pathophysiology and its association with lipid metabolism may explain a new mechanism of PCOS occurrence that is related to metabolic dysfunctions. The aim of this study is to understand the correlation between the interleukin profile (levelsof IL-6, IL-10, IL-18, IL-29, IL-33 and TNF-α) with the lipid profile and anthropometric data in obese PCOS Iraqi women in comparison with obese, apparently healthy, women.

Materials and Methods

Participants

One hundred women with obese PCOS were selected from Kamal Al-samurai Teaching Hospital in Baghdad through the period from December 2017 to June 2018, according to diagnosis that was based on the 2003 Rotterdam ESHRE/ASRM criteria modified by Aziz and co-workers[11, 2]. The range of age of the women with PCOS patients enrolled in the study had an age range of 18-39 years and a body mass index (BMI) range of29-33 Kg/m^2. In addition, a group of seventy five age and BMI-matching obese healthy women without PCOS were recruited as a control group.

Demographic data

Standard anthropometric data and medical history were obtained from each subject after explaining the nature, purpose, and duration of the study. BMI for each patient included measurement of height and weight (kg/m^2, which were scored to classify the state of obesity. A subject with a BMI of < 18.5

was considered underweight, normal was under 18.5-24.9,25-29.9 was considered overweight, and > 30 as obese [12].Waist-to-hip ratio (WHR) was calculated based on the ratio between the standing waist and hip circumference,with WHR value> 0.8 considered as abnormal[13].The hirsutism score was determined using the modified Ferriman and Gallwey scoring system. This system grades terminal hair growth on a scale from 0 (no terminal hairs) to 4 (extensive terminal hair growth) on 9 anatomical sites (upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, and thigh,) and uses the sum of nine areas to generate an overall hirsutism score. A patient's score may therefore range from 0 to a score of 36, while a score of ≥ 8 indicates hirsutism [14].

Biochemical measurements

Blood samples were collected in clot activator tube from all subjects during the 3–5 days after spontaneous menstruation. Serum was separated and kept frozen until time of analysis**.**Glucose and lipid profilewere determined using commercial kits from Sinreact company(spain). Serum insulin, testosterone, sex hormone binding globulin (SHBG), hs-CRP, and interleukins(IL-6, IL-10,IL-18,IL-29,IL-33,TNF-alpha) were measured using human ELISA kits from Abcam company(USA).Free androgen index(FAI)was calculated as follows: FAI = serum total testosterone/serum SHBG × 100. Homeostasismodel assessment of insulin resistance (HOMA-IR) index was calculated by the following formula [15]: HOMA-IR = Fasting blood glucose × fasting insulin/22.5

Statistical analysis

Data were expressed as a M ± SE, while independent t-test, spearman test and ANOVA table were used to express significant differences at probability level of 0.05 using the computer program IBM SPSS version 23.0.

Results and Discussion

Demographic and clinical characteristics of the study participants

Data from Table-1 show the clinical characteristics of all obese women enrolled in the study, with regard to the diagnostic criteria of PCOS. According to the criteria, for women to be diagnosed with PCOS,2 or 3 of the following features must be present: oligo or amenorrhea, clinical or biochemical androgen excess, and ultrasonic polycystic ovarian morphology \.Women in all groups enrolled in the current study were matching in age and BMI. However, clinically- there were significant ($p< 0.05$) elevations in the scoring of hirsutism and WHR, as well as higher proportions of menstrual irregularity and acne in OPCOS women in comparison with the control group.OPCOS women demonstrated comparable clinical, metabolic and biochemical characteristics at baseline, with about 88% were less than 36 years of age. These results are in agreement with those previously reported [16], in which prevalence of PCOS was higher in younger women (<35 years of age) than in older women (> 35years of age). These age stages were related with physiological changes including decline of the follicular cohort after the age of 35.

Table 1-Clinical and demographic characteristics of PCOS and non PCOS women (Mean±SE)

Characteristics	Control Group No:75	PCOS group No=100	P Value
Age (year)	28.75±0.72	29.12±0.33	>0.05
BMI(Kg/m^2)	30.94±0.35	31.11±0.46	>0.05
WHR	0.70±0.01	0.86±0.02	<0.05
Menstrual irregularity	11	81	<0.001
Hirsutism score	4.11±0.21	8.92±0.36	<0.001
Acne	8	34	<0.001

The mean ± SE of BMI in OPCOS patients and obese non PCOS healthy women in this work was 31.11±0.46 and 30.94±0.35 kg/m^2, respectively, indicating no statistically significant difference ($p>0.05$) between the two groups which were both considered as obese (BMI >30 kg/m^2). This finding is in a close agreement with that described by another study in Iraqi patients [16] in which about 63% of PCOS women were found to be overweighed or obese. However, the proportion of obese patients in our study is higher than that reported by Bulent and his co-workers who found that about 50 % of

PCOS cases are overweight or obese [17].On the contrary, Herriot *et al* found that 66% of cases with PCOS were below 24.9 Kg/m^2 BMI[18].Indeed, there is a wide variability in the prevalence of obesity and overweight in PCOS cases across different countries. Highest obesity prevalence was demonstrated in studies conducted in the United States and Australia, with 61% to 76% of women with PCOS being considered obese [19]. However, the global increase of obesity may play a significant role in the development of PCOS in sensitive individuals, iincluding the impact of obesity on reproduction in PCOS women [20].

Obesity, particularly the central visceral obesity as indicated by an increased WHR ratio, is a risk factor in a woman with PCOS to be diabetic with heart disease, while it also worsens the clinical manifestation (anovulation, hyperandrogenism and insulin resistance) of the syndrome as compared with healthy women. OPCOS women in the current study had significantly higher values of WHR (0.86± 0.08 versus 0.70 ± 0.06 in healthy women), which is compatible with other studies which observed abdominal obesity in women with PCOS as determined by having a WHR of 0.85 or greater [21,22]. Yasir and his co-workers found that Iraqi women with PCOS had significantly higher WHR values as compared to the control [23].

The early and dominant symptom of the anovulatory component of PCOS is the menstrual cycle disorder. The incidence of cycle disorder in women with PCOS seems to be quite variable [24]. In the current study, about 81% of women with OPCOS were with oligomenorrhea compared to 11% in healthy women. Al-Bayati[25] found that 72.5% of Iraqi women with PCOS had oligomenorrhea and/ or amenorrhea and this is in contrast to the results reported by other studies in which 59.9% of PCOS patients were with oligomenorrhea.This variation in the incidence of menstrual irregularity among women with PCOS may be due to ethnic differences among the patients as well as variability in definition and criteria used for diagnosis of PCOS among different studies. In a wide spectrum of patients diagnosed by varying criteria, 75–85% of PCOS women demonstrated clinically evident menstrual irregularity [26,27].

In the present study 34%of patients with PCOS had hirsutism and 8 % had acne. These results are in a close agreement with previously reported data[17] in which about 64.49% of patients were suffering from hirsutism. In a meta-analysis by Azziz and his co-workers [28], the cumulative incidence of hirsutism was approximately 60% in PCOS patients,which might resulted from the cooperative influence of increased androgen production within the pilosebaceous unit [29].Androgens participate in the development of acne by stimulating sebum production, thereby providing optimal conditions for bacterial colonization with organisms such as *Propionibacterium acnes* [30].On the other hand, the cardinal feature of PCOS is hyperandrogenism which can be demonstrated by clinical signs including hirsutism and acne, and biochemically by measuring the serum androgens levels, including testosterone, androstenedione and androgen precursor DHEAS [27].

Metabolic parameters in PCOS

Data from Table-2 show the mean levels of blood sugar, insulin, HOMA-IR, total cholesterol, HDL, LDL, VLDL, and TG in OPCOS women and healthy obese non PCOS women. With respect to the blood sugar measured, OPCOS women had higher mean value (115±2.4mg/dl)in comparison with 95±1.9 mg/dl in healthy non PCOS women, but this the difference was insignificant.Insulin concentration was significantly higher ($P<0.05$) in OPCOS women (16.8±1.4 µIU/ml) in comparison to 7.2±1.03 µIU/ml in obese non PCOS women.In addition,HOMA-IR value was also significantly higher ($P<0.05$) in OPCOS women 93.5±0.3) in comparison to 2.1±0.2 in obese non PCOS women. As related to the metabolic appearance of PCOS cases in this work, data showed that about seventy five percent of obese PCOS patients had IR, as indicated by measuring HOMA-IR which provides a mathematical mean for estimating insulin resistance. This result agrees well with other studies which found that obese PCOS women had significantly high fasting insulin status and slightly elevated fasting glucose in comparison to control[31].

Moreover, significantly higher levels of total testosterone and free androgen index were found in OPCOS women in comparisons with healthy obese non PCOS women, as showed in Table-2.SHBG levels were significantly lower ($P<0.01$) in OPCOS compared with the obese healthy women group. Furthermore, FAI was significantly higher in OPCOS women with HOMA-IR compared with healthy non PCOS women ($P< 0.01$). Data from the current work suggest that androgen excess demonstrated by high FAI status might serve as an indicator of a prediabatic status, which might induce insulin resistance in PCOS women [31].

Table 2-Mean of biochemical parameters (M±SE) in healthy and PCOS groups.

Variable	Control group	PCOS group	p value
B. sugar (mg/dl)	95±1.9	115±2.4	> 0.05
insulin (µIU/ml)	7.2±1.03	16.8±1.4	<0.05
HOMA-IR	2.1±0.2	3.5±0.3	<0.05
T. Testosterone(ng/ml)	0.55±0.09	1.12±11	P<0.01
SHBG (nmole/l)	59±6.2	34±4.5	P<0.01
FAI	2.21±0.23	4.12±0.40	P<0.05
HDL (mg/dl)	46.5±2.3	39.3±2.5	<0.05
LDL (mg/dl)	112.2±1.9	136.1±2.3	<0.05
VLDL (mg/dl)	16.0±1.1	24.1±1.2	<0.01
TG (mg/dl)	135.3±6.1	180.2±7.5	<0.001

Interleukin levels in PCOS

Data in Table-3 illustrate that mean serum levels of IL-6 in obese PCOS patients were higher (46.1±3.75pg/ml) in comparison with 22.5±2.46 pg/ml in control women. In addition, mean serum IL-10 levels were also higher in OPCOS women (418.2±25.8 pg/ml) compared to 315.7±22.5 pg/ml in healthy non obese women.

Results from the current work suggest that serum IL-18 concentration was higher (287 ± 14pg/ml) in OPCOS women in comparison with 233±12 pg/ml in non PCOS women. Since OPCOS patients demonstrated an elevated WHR value(higher than 0.86) and declined insulin sensitivity, the increase in mean serum IL-18 concentration established in OPCOS is possibly related to the visceral adiposity and IR, regularly noticed in OPCOS patients. Considering that IL-18 is an initial moderator in the inflammatory pathway, serum IL-18 levels can be speculated as a hypersensitive marker of the continuous inflammatory action essential in IR.

In reverse to other research attempts related to other cardiovascular risk markers such as serum CRP or IL-6 levels that build upon mostly on obesity in imaginary agreement with the improvement of adipose tissue to the excretion of inflammatory cytokines[32-35].

Table 3-Interleukins and C-reactive protein (M±SE) levels in Obese PCOS and healthy women

Parameter	Control Group	PCOS Group	P value
IL-6 pg/ml	22.5±2.46	46.1±3.74	P<0.01
IL-10 pg/ml	315.7±22.3	418.2±25.8	P<0.01
IL-18 pg/ml	233±12	287 ± 14	p<0.01
IL-27 pg/ml	2.5±0.12	6.9±-.23	P<0.01
IL- 33 pg/ml	5.7±0.91	11.9±1.1	P<0.01
TNF-α pg/ml	10.5±1.2	31.3±1.9	P<0.01
hs-CRP (mg/L)	1.34±0.11	5.45±0.87	P<0.01

The correlation of IL-18 levels with BMI of OPCOS had a value of r= 0.34(P<0.01, whereas that value with WHR was r= 0. 40, (P<0.01) proposing that IL-18 may be originated by the adipose tissue. Hence, it is also probable that higher mean serum IL-18 levels found in OPCOS women were only a result of the main visceral deposition of fat associated with the PCO syndrome, rather than having any pathogenic role. Finally, various evidence proposed that IL-18 is implicated in the pathogenesis of atherosclerosis and may help as a cardiovascular risk marker[35].Therefore, the higher serum IL-18 levels associated with OPCOS might be related to subclinical atherosclerosis in these patients, as proved by significant differences in the values of all components of lipid profile , such as Chol, TG, HDL, and LDL(Table-2).

The finding of elevated circulatory IL-18 might be interpreted by many assumptions. 1) Adipose tissue, mainly visceral fat, might produce IL-18, illustrating the higher levels of serum IL-18 status observed in OPCOS women with visceral adiposity in comparison to healthy controls and lean individuals. 2) Given the valuable information related to the action of the inflammatory cytokines through paracrine and autocrine actions to promote IR [35], IL-18 might also be involved in the pathogenesis of IR, associated with its high levels in PCOS women. 3) Elevation in serum IL-18 level might be due to early atherosclerotic changes. 4) Genetic alterations in the gene encoding IL-18 might be correlated with PCOS, obesity, and IR [36, 37]. In conclusion, obesity and PCOS promote elevation in mean serum IL-18 level, which is also connected with different signs of global and visceral adiposity and with IR. The actual mechanisms underlying this correlation need more studies to be discovered.

Results from Table- 3 demonstrate that mean serum IL-29 levels were significantly higher (P<0.01) in OPCOS than those in obese non PCOS women. To investigate the association between serum IL-29 levels and lipid metabolism in OPCOS women, Spearman's correlation analysis was performed and the results showed that the high serum IL-29 levels were positively correlated with increased T.Chol (r = 0.52, *P*<0.005), TG (r =0.57, *P*<0.001), and LDL-C (r=0.60, *P*<0.001), while negatively correlated with HDL-C (r= -0.64, *P*<0.001). Data from Table-4 suggest a closer association between mean serum IL-29 level and lipid metabolism in OPCOS as compared to that in obese non PCOS control women.The results also demonstrated that mean serum IL-29 level was higher in PCOS patients and that it may act as one of the pathogenic factors for PCOS. Altered cytokine expression has been demonstrated to be related to PCOS and it could be used to classify PCOS. Therefore, the diagnostic association between IL-29 and values of each of BMI,WHR, testosterone, and HOMI in PCOS were evaluated, as shown in Table-4.

Our observations suggest that IL-29 may be useful in improving the diagnostic performance of testosterone in PCOS detection. Furthermore, mean serum IL-29 level was positively correlated with Chol, TG and LDL-C, while negatively correlated with HDL-C in PCOS patients.Therefore,IL-29 and its contribution to the clinical syndrome of PCOS patients reflected the lipid metabolism states and the risk of developing cardiovascular diseases in these patients.. This correlation provided a new vision into the prognosis of PCOS, where the combination of IL-29 and testosterone increased the accuracy of PCOS detection. Also, IL-29 was closely correlated with HDL-C, giving it the possibility to serve as a novel predictor for the risk of cardiovascular diseases in PCOS patients[10]. Therefore, understanding the role of IL-29 in metabolic disorders would allow us to better understand the etiology of PCOS.

Table 4-Correlation coefficient between IL-29 and anthropometric and biochemical parameters

Parameter	R	P
BMI	**0.44**	**<0.01**
WHR	**0.50**	**<0.001**
Chol	**0.52**	**< 0.005**
TG	**0.57**	**<0.001**

HDL	**- 0.64**	**<0.001**
LDL	**0.60**	**<0.001**

Data in Table-3 demonstrate significantly higher mean serum levels of IL-33 in OPCOS women as compared to obese non PCOS women (11.9±1.1 and 5.7±0.91 pg/ml, respectively).A positive correlation was found between IL-33 and each of WHR,BMI and lipid profile(r= 0.41 ,P<0.001; r= 0.52 ,p< 0.001;r= 0.40,p< 0.001, respectively). In addition, the results demonstrated correlation coefficients of 0.48 (*P*<0.01) for Chol, 0.52 (*P*<0.001) for TG,and 0.57 (*P*<0.001) for LDL-C.Furthermore, IL-33level was negatively associated with good cholesterol (r =-0.66, *P*<0.001).These data (Table-5) are compatible with previously reported results[38].It seems that hyperandrogensim in OPCOS women is correlated with IL-33 levels and that it is an important factor in the increase of these levels.Therefore,we conclude that OPCOS women who are complicated with IR have higher serum levels of IL-33,which might be considered as a novel cytokine involved in PCOS pathogenesis [39, 40].

Table 5-Correlation coefficient between IL-33 and anthropometric and biochemical parameters

Parameter	R	P
BMI	**0.41**	**<0.001**
WHR	**0.52**	**<0.001**
Chol	**0.48**	**< 0.01**
TG	**0.52**	**<0.001**
HDL	**- 0.66**	**<0.001**
LDL	**0.57**	**<0.001**

Mean serum levels of TNF-α were significantly higher (P<0.01) in OPCOS women (31.5±2.3 pg/ml) as compared to that in obese non PCOS women (10.5±1.9 pg/ml). Data from the current work are in a good agreement with many other studies which indicated that mean serum levels of TNF-α in patient with PCOS is higher than that in the control women . However, several studies attributed an increased level of TNF-α to obesity [40], while other studies reported higher levels of TNF-α in PCOS women independent of obesity [41].

According to the study of Gonzalez and colleagues, a surge in the secretion of TNF-α in OPCOS woman is linked to IR and hyperandrogenism. Thus, a change in mean serum levels of TNF-α may be due to IR, which was considered as a common complication in patients with OPCOS [41]. Whether the rise in mean serum TNF-α levels in PCOS is agenetic feature of this syndrome or it occurs due to obesity or insulin resistance is a question that needs further investigation. The circulatory TNF-α levels in OPCOS women might act on the development of IR and androgen oversupply of PCOS,suggesting that high serum TNF-α levels are related to IR and androgen excess but not to the BMI. Hence, a high TNF-α level is not an elemental characteristic of PCOS, but it might actlike IL-6 in promoting IR and hyperandrogenism of PCOS[42].

Finally, levels of the low grade inflammatory marker hsCRPwere higher in OPCOS women (6.4±1.1 mg/dl) in comparison with 2.3±0.9 mg/dl in non PCOS control women. These results are in agreement with that reported by Yeh and his co-workers in 2001, who demonstrated that OPCOS patients had significantly elevated levels of hsCRP compared to weight matched controls. hsCRP is secreted in response to cytokines. including IL-6, and increased hs CRP level is a strong invariant predictor for the risk of cardiovascular events [43].

In conclusion, adiposity in PCOS may induce an elevation in serum levels of interleukins, which is also connected with changes in many indexes of global and visceral adiposity and complicated with IR. These data may provide a novel insight into the pathogenesis of the metabolic syndrome related to

PCOS and the assessment of the risk of cardiovascular diseases in obese PCOS women. The precise mechanisms involved in these correlations require further studies.

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