Assessment of serum chemerin, vaspin and omentin-1 levels in patients with polycystic ovary syndrome

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Abstract

Objective: To determine serum chemerin, vaspin and omentin-1 in overweight and normal weight patients with polycystic ovary syndrome (PCOS) and investigate the possible relationship between these adipokines and metabolic syndrome.

Methods: This cross sectional study enrolled women with PCOS and healthy women. Serum chemerin, vaspin and omentin-1 were assessed by enzyme-linked immunosorbent assay methods.

Results: Forty patients with PCOS and 30 healthy controls were included in the study. In the PCOS group, 18 women were overweight (body mass index [BMI] = 25.0–29.9 kg/m^2) and 22 had normal weight (BMI = 18.5–24.9 kg/m^2). Chemerin, total cholesterol, dehydroepiandrosterone sulphate and free androgen index (FAI) were significantly higher; and high-density lipoprotein cholesterol and sex hormone binding globulin were significantly lower in overweight PCOS patients compared with normal weight PCOS patients. A positive correlation was found between chemerin and BMI, triglyceride, insulin, homeostatic model assessment of insulin resistance and FAI in the PCOS group. There was no difference in serum chemerin, vaspin and omentin-1 between PCOS patients and healthy controls.

Conclusion: Circulating chemerin was increased in overweight compared with normal weight PCOS patients. The most predictive variables for circulating chemerin in PCOS patients were BMI, FAI and age.

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Introduction

Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder in women of reproductive age and, in some patients, presents with abdominal adiposity and dyslipidaemia.[1] Although genetic, environmental and behavioural factors are related to the development of PCOS, its aetiology remains to be elucidated.[1,2] The risk of metabolic syndrome is four-times higher in PCOS patients than in non-PCOS patients.[3] Metabolic syndrome and PCOS share many common features such as insulin resistance, abdominal obesity, risk of type 2 diabetes mellitus (T2DM) and dyslipidaemia.[2,3]

Adipose tissue secretes adipokines such as chemerin, vaspin and omentin-1.[4] These adipokines are thought to be involved in the development of metabolic syndrome and its related diseases including obesity, T2DM and cardiovascular disease.[5] Increased plasma levels of chemerin have been observed in patients with newly onset metabolic syndrome and positive correlations have been found between chemerin and body mass index (BMI), homeostatic model assessment of insulin resistance (HOMA-IR) and triglyceride and negative correlations with high-density lipoprotein cholesterol (HDL-C).[6–8] Additionally, chemerin levels have been shown to be high in obese PCOS women with insulin resistance.[9,10] Although vaspin improves insulin sensitivity in mice,[11] its effects on insulin sensitivity and BMI in humans is unclear,[12,13] and in PCOS patients it has shown inconsistent results.[14,15] In contrast, increased circulating levels of omentin-1 have been observed following weight loss-induced improvement in insulin sensitivity.[16,17] Decreased omentin-1 levels were reported in pre-diabetic patients, those with type 1 diabetes mellitus and those with newly diagnosed, untreated T2DM.[18]

Polycystic ovary syndrome and metabolic syndrome related parameters such as insulin and adipokines have been investigated in obese and insulin resistant patients.[2,5] However, there are limited data from overweight and normal weight PCOS patients. Therefore, the aim of this study was to determine serum chemerin, vaspin and omentin-1 concentrations in overweight and normal weight PCOS patients and healthy women and to investigate the possible relationship between these adipokines and metabolic syndrome.

Patients and methods

Study population

This study was cross sectional and performed in the Department of Obstetrics and Gynaecology at Celal Bayar University Hospital, Manisa, Turkey. The study consecutively recruited women with PCOS and healthy women (controls) who met the inclusion and exclusion criteria. The control group consisted of women who had visited the clinic for non-hormonal or non-menstrual irregularities. The Rotterdam criteria were used for the diagnosis of PCOS.[19] Women with at least two of the following were included in the PCOS group: oligo/anovulation; clinically apparent or biochemically verified hyperandrogenism; typical ovarian morphology on pelvic ultrasonography. Transabdominal ultrasonography was performed in those who could not be examined vaginally. Ultrasonography (Siemens® cce71-mt2; Siemens, Erlangen, Germany) and Ferriman Gallywey scoring were performed by the same investigator (A.G.).[20] Exclusion criteria for all subjects included: obesity (BMI > 30 kg/m^2); pregnancy; cardiovascular disease; thyroid function disorder; malignancy; hypertension; renal dysfunction; other endocrine pathologies leading to hyperandrogenism. None of the patients had used oral contraceptives, glucocorticoids, ovulation induction agents, anti-obesity drugs or any other steroid containing drug for the last 2 months.

The study was approved by the local ethics committee of Faculty of Medicine,

Celal Bayar University (01.11.2010/0019) and informed consent was obtained from all women. The study adhered strictly to the Declaration of Helsinki principle 2008.

Biochemical assessments

Venous blood samples were obtained by one investigator (Y.G.) from all participants after overnight fasting in the early follicular menstrual phase. Serum chemerin, vaspin and omentin-1 concentrations were analysed by enzyme-linked immunosorbent assay (ELISA) method using commercial reagents (human chemerin, Millipore, Billerica, MA, USA; human vaspin, Adipogen, Liestal, Switzerland; human omentin-1, Enzo Life Sciences, Farmingdale, NY, USA). The intra-assay percentage coefficients of variation (CV) for chemerin, vaspin and omentin-1 were 5.0%, 2.7% and 5.7%, respectively. The inter-assay CV for chemerin, vaspin and omentin-1 were 5.0%, 6.05% and 6.07%, respectively. Glucose, triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and HDL-C levels were analysed using commercial reagents (Unicel DXC 800, Beckman Coulter, Brea, CA, USA). Insulin, total testosterone, dehydroepiandrosterone sulphate (DHEAS) and sex hormone binding globulin (SHBG) were measured by chemiluminescence (DXI-800, Beckman Coulter; Immulite 2000, Siemens). Free testosterone and 17-OH-progesterone were analysed by radioimmunoassay using commercial reagents (Immunotec A, Beckman Coulter). Insulin resistance (IR) was calculated according to HOMA-IR = [fasting insulin (μU/ml) × fasting glucose (mmol/l)]/22.5 formula.[21] HOMA-IR ≥ 2 was used as a diagnostic criterion for insulin resistance.[22] The formula for BMI = body weight/height^2 (kg/m^2). Free androgen index (FAI) was calculated according to FAI = (total testosterone/SHBG) X 100 formula.[23]

Statistical analyses

All statistical analyses were performed using the SPSS® statistical package, version 15.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Numerical data were tested for normality by Kolmogorov–Smirnov test. Student's t-test and Mann–Whitney U-test were used to compare group means. Analysis of covariance was used to compare means adjusting for age. Pearson's correlation analysis was used to evaluate the relationship between chemerin and other parameters. A multivariate regression analysis was used to identify independent predictors of circulating serum chemerin in patients with PCOS and controls. Type 1 error was 5% and a P-value < 0.05 was considered to indicate statistical significance.

Results

Forty women with PCOS and 30 healthy women were included in this cross sectional study. The women were divided into subgroups of normal weight (BMI = 18.5–24.9 kg/m^2) and overweight (BMI = 25.0–29.9 kg/m^2). In the PCOS group, 18 women were overweight and 22 had normal weight and in the healthy control group 13 were overweight and 17 had normal weight. Clinical, hormonal and metabolic features of the PCOS patients and healthy controls are shown in Table 1. Table 2 shows the same parameters for overweight and normal weight patients with PCOS.

The healthy controls were significantly older than PCOS patients ($P = 0.001$) (Table 1). Total cholesterol, LDL-C, total testosterone, free testosterone and FAI were statistically significantly higher ($P = 0.04$, $P = 0.022$, $P = 0.001$, $P = 0.002$ and $P = 0.039$, respectively) in PCOS patients than in controls. There was no significant difference between the two groups for BMI, glucose, triglyceride, HDL-C, insulin, HOMA-IR, DHEAS, SHBG, 17-OH progesterone, vaspin, omentin-1 and chemerin.

Table 1. Clinical, hormonal and metabolic features of the women with polycystic ovary syndrome (PCOS) and healthy control women included in this cross sectional study.

Parameter	PCOS women $n = 40$	Healthy control women $n = 30$	Statistical significance[a]
Age, years[b]	25.40 ± 5.62 (23.60, 27.19)	31.50 ± 7.59 (28.66, 34.33)	P = 0.001
BMI, kg/m^2	24.87 ± 5.02 (23.14, 26.59)	23.7 ± 4.46 (22.05, 25.39)	NS
Glucose, mmol/l	4.92 ± 0.45 (4.78, 5.07)	5.02 ± 0.67 (4.77, 5.27)	NS
Triglyceride, mmol/l	1.42 ± 1.25 (1.06, 1.78)	1.36 ± 0.70 (1.09, 1.62)	NS
Total cholesterol, mmol/l	4.72 ± 1.14 (4.34, 5.07)	4.50 ± 0.82 (4.19, 4.81)	P = 0.040
HDL-C, mmol/l	1.45 ± 0.42 (1.31, 1.58)	1.45 ± 0.259 (1.35, 1.55)	NS
LDL-C, mmol/l	2.61 ± 0.81 (2.35, 2.87)	2.43 ± 0.66 (2.18, 2.67)	P = 0.022
Insulin, pmol/l	59.72 ± 34.03 (49.03, 71.19)	52.71 ± 27.28 (42.16, 63.19)	NS
HOMA-IR	1.92 ± 1.20 (1.53, 2.30)	1.68 ± 0.95 (1.33, 2.04)	NS
Total testosterone, nmol/l	2.00 ± 0.73 (1.73, 2.22)	1.14 ± 0.55 (0.93, 1.35)	P = 0.001
Free testosterone, pmol/l	7.01 ± 3.64 (5.86, 8.19)	4.19 ± 1.87 (3.47, 4.89)	P = 0.002
DHEAS, μmol/l	6.38 ± 3.23 (5.35, 7.42)	4.55 ± 2.73 (3.70, 5.40)	NS
SHBG, nmol/l	59.98 ± 43.07 (46.20, 73.75)	64.10 ± 39.90 (49.20, 78.99)	NS
17-OH progesterone, nmol/l	3.72 ± 3.63 (2.51, 4.90)	3.74 ± 2.72 (2.72, 4.75)	NS
FAI	5.39 ± 4.64 (3.90, 6.87)	2.72 ± 2.81 (1.67, 3.76)	P = 0.039
Vaspin, ng/ml	0.11 ± 0.05 (0.09, 0.12)	0.10 ± 0.08 (0.07, 0.13)	NS
Omentin-1, ng/ml	185.89 ± 53.47 (168.79, 203.00)	180.77 ± 40.59 (165.61, 195.93)	NS
Chemerin, ng/ml	65.87 ± 19.64 (59.59, 72.15)	67.15 ± 11.57 (62.83, 71.48)	NS

Data presented as mean ± SD (95% confidence interval).
[a]Analysis of covariance adjusted for age.
[b]Student's t-test.
BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; DHEAS, dehydroepiandrosterone sulphate; SHBG, sex hormone binding globulin: FAI, free androgen index; NS, no significant between-group difference ($P \geq 0.05$).

The HOMA-IR values for both groups indicated that there was no evidence of insulin resistance.

Overweight patients with PCOS were statistically significantly older than normal weight PCOS patients ($P = 0.008$) (Table 2). Serum chemerin, total cholesterol, DHEAS and FAI were significantly higher ($P = 0.008$, $P = 0.042$, $P = 0.046$, $P = 0.030$, respectively), and HDL-C and SHBG were significantly lower ($P = 0.001$, $P = 0.040$, respectively) in overweight PCOS patients compared with normal weight PCOS patients. However, there was no significant difference between the two groups for glucose, triglyceride, LDL-C, insulin, HOMA-IR, total testosterone, free testosterone, 17-OH progesterone, vaspin and omentin-1. No significant difference was found between normal and overweight controls in serum chemerin, vaspin and omentin-1 levels (data not shown).

There was no correlation between either serum omentin-1 or vaspin with other parameters in PCOS patients (data not shown). There was a positive correlation between serum chemerin and age ($P = 0.016$), BMI ($P = 0.001$), triglyceride ($P = 0.006$),

Table 2. Clinical, hormonal and metabolic features of overweight (BMI = 25.0–29.9 kg/m^2) and normal weight (BMI = 18.5–24.9 kg/m^2) women with polycystic ovary syndrome (PCOS).

Parameter	Normal weight PCOS women $n = 22$	Overweight PCOS women $n = 18$	Statistical significance[a]
Age, years	21.0 (16.0–38.0)	26.50 (22.0–38.0)	$P = 0.008$[b]
Glucose, mmol/l	4.94 (3.27–5.88)	4.88 (4.38–5.60)	NS
Triglyceride, mmol/l	0.97 (0.38–4.05)	1.26 (0.23–5.39)	NS
Total cholesterol, mmol/l	4.32 (3.28–7.71)	4.49 (3.13–6.06)	$P = 0.042$
HDL-C, mmol/l	1.48 (1.04–2.77)	1.21 (0.77–1.53)	$P = 0.001$
LDL-C, mmol/l	2.52 (1.50–4.58)	2.67 (1.39–3.70)	NS
Insulin, pmol/l	45.07 (15.97–153.55)	57.50 (12.08–154.45)	NS
HOMA-IR	1.51 (0.48–5.78)	1.84 (0.37–4.94)	NS
Total testosterone, nmol/l	1.98 (0.45–3.89)	1.77 (0.73–3.16)	NS
Free testosterone, pmol/l	5.69 (2.81–13.15)	6.73 (3.01–16.72)	NS
DHEAS, μmol/l	4.99 (1.59–10.91)	5.92 (3.22–16.07)	$P = 0.046$
SHBG, nmol/l	58.80 (23.0–180.0)	36.50 (11.60–180.0)	$P = 0.040$
17-OH progesterone, nmol/l	3.76 (0.70–23.60)	2.30 (0.96–7.24)	NS
FAI	3.54 (0.71–11.15)	4.77 (0.85–22.44)	$P = 0.030$
Vaspin, ng/ml	0.11 (0.05–0.23)	0.10 (0.05–0.37)	NS
Omentin-1, ng/ml	180.40 (94.48–239.65)	206.30 (165.61–195.93)	NS
Chemerin, ng/ml	55.83 (38.49–91.54)	73.05 (47.52–119.03)	$P = 0.008$

Data presented as median (interquartile range).
[a]Analysis of covariance adjusted for age.
[b]Mann–Whitney *U*-test.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; DHEAS, dehydroepiandrosterone sulphate; SHBG, sex hormone binding globulin: FAI, free androgen index; NS, no significant between-group difference ($P \geq 0.05$).

insulin ($P = 0.003$), HOMA-IR ($P = 0.042$) and FAI ($P = 0.002$); and an inverse correlation between chemerin and HDL-cholesterol ($P = 0.018$) in PCOS patients (Table 3). In the control group, there was a positive correlation between chemerin and BMI and triglyceride (data not shown).

The variables that were significantly correlated with serum chemerin were entered into a multivariable regression analysis model with the exception of triglyceride, insulin and HDL-C because they are strongly/moderately correlated with BMI. Analysis of data from PCOS patients and controls showed that age ($P = 0.005$), BMI ($P = 0.011$) and FAI ($P = 0.007$) were independent predictors for circulating chemerin (Table 4). The value for R^2 was 0.337 (i.e.,

33.7% of the variability in serum chemerin was accounted for by knowing age, BMI and FAI).[24]

Discussion

Obesity and insulin resistance are both strongly and independently associated with metabolic syndrome in patients with PCOS but androgen status was not associated.[25] However, there is evidence to show that metabolic syndrome is 1.5-times more likely in morbidly obese women with hyperandrogenaemia even in the absence of PCOS.[26] High levels of insulin, HOMA-IR, triglyceride, testosterone, FAI,[9,14,27,28] and low levels of HDL-C and SHBG have been observed in obese PCOS patients.[14,27,28] Similarly, high

Table 3. Pearson's correlation coefficient analysis of the possible correlation between chemerin and other parameters in women with polycystic ovary syndrome ($n = 40$).

Parameter	Pearson's correlation coefficient	Statistical significance
Age, years	0.377	$P = 0.016$
BMI, kg/m^2	0.532	$P = 0.001$
Glucose, mmol/l	−0.006	NS
Triglyceride, mmol/l	0.426	$P = 0.006$
Total cholesterol, mmol/l	0.256	NS
HDL-C, mmol/l	−0.371	$P = 0.018$
LDL-C, mmol/l	0.286	NS
Insulin, pmol/l	0.338	$P = 0.033$
HOMA-IR	0.324	$P = 0.042$
Total testosterone, nmol/l	0.146	NS
Free testosterone, pmol/l	0.227	NS
DHEAS, µmol/l	0.237	NS
SHBG, nmol/l	−0.030	NS
17-OH progesterone, nmol/l	−0.188	NS
FAI	0.469	$P = 0.002$
Vaspin, ng/ml	−0.190	NS
Omentin-1, ng/ml	0.017	NS

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; DHEAS, dehydroepiandrosterone sulphate; SHBG, sex hormone binding globulin: FAI, free androgen index; NS, no significant difference ($P \geq 0.05$).

levels of testosterone,[29] FAI,[28,29] insulin and low levels of HDL-C and SHBG[28] have been reported in overweight PCOS patients. Additionally, in non-obese (i.e., BMI < 25 kg/m^2) PCOS patients, insulin and HOMA-IR levels were also higher than in normal healthy controls.[10] The present study found high levels of total cholesterol, LDL-C, total testosterone, free testosterone and FAI in all PCOS patients. In overweight (BMI $= 25.0$–29.9 kg/m^2) PCOS patients, serum cholesterol, DHEAS and FAI were significantly higher than in

normal weight PCOS patients, but HDL-C and SHBG were significantly lower. These findings are supported by other studies that have shown that PCOS is associated with metabolic, endocrine and dyslipidaemic disorders.[3,14,28,29]

Circulating levels of adipokines have been shown to change in metabolic disorders.[30] For example, plasma omentin-1 levels have been shown to be inversely correlated with insulin resistance and highly correlated with HDL in obese patients.[31] In addition, low circulating omentin-1 levels have been found in PCOS patients with insulin resistance,[27,32] which suggests that they may be associated with low insulin sensitivity. Decreased omentin-1 and increased androgen levels have been observed in non-obese women with PCOS and postprandial hyperinsulinaemia and hyperglycaemia lead to lower omentin-1 levels compared with the fasting state.[29] Research has found that omentin-1 levels were significantly lower in PCOS patients compared with healthy controls[33] and this relationship was not related to obesity.[28] In contrast, other studies have found no significant difference in omentin-1 levels between PCOS patients and controls.[14,34] In the present study, no difference was observed in serum omentin-1 concentrations between PCOS patients and controls or between the normal weight and overweight PCOS subgroups. Therefore, these current findings are similar to others and support the hypothesis that PCOS is related to androgen levels and lipid disorders but not to circulating omentin-1 levels.[14,34]

Elevated levels of serum vaspin and fat tissue vaspin are correlated with obesity, insulin resistance and T2DM.[11,12] However, the exact relationship between vaspin secretion, insulin sensitivity and defects in glucose metabolism remains to be elucidated. Increased vaspin expression may be an intrinsic compensatory mechanism in fat tissue as a reaction to impaired glucose

Table 4. Multivariate regression analysis of independent predictors of serum chemerin levels in women with polycystic ovary syndrome ($n = 40$) and healthy controls ($n = 30$).[a]

Parameters	Coefficient (β)	Standard error	Statistical significance
Age	0.720	0.247	$P = 0.005$
BMI	0.975	0.370	$P = 0.011$
HOMA-IR	0.406	1.626	NS
FAI	124.676	44.546	$P = 0.007$
Intercept of the regression line	16.449	9.173	NS

[a]The variables that were significantly correlated with serum chemerin were entered into a multivariable analysis model with the exception of triglyceride, insulin and high-density lipoprotein cholesterol because they are strongly/moderately correlated with BMI.
BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; FAI, free androgen index; NS, no significant difference ($P \geq 0.05$).

metabolism or decreased insulin sensitivity.[35] Varied results have been obtained from studies investigating the relationship between vaspin and PCOS. For example, one study reported elevated levels of vaspin in PCOS patients and found that neither weight loss nor metformin affected vaspin concentrations.[36] In two other studies, increased vaspin levels were observed in overweight/obese PCOS patients with insulin resistance.[27,37] A common factor of these three studies appears to be overt insulin resistance.[27,36,37] In contrast, no difference in serum vaspin levels was found between PCOS patients with insulin resistance and controls in two other studies.[14,38] In the present study, there was no statistically significant difference in serum vaspin between PCOS patients and controls or between overweight and normal weight PCOS patients. Interestingly, the patients in the PCOS group did not have insulin resistance, which may explain the lack of effect on vaspin levels.

Chemerin regulates insulin sensitivity and insulin secretion and, reciprocally, insulin stimulates chemerin secretion from adipose tissue.[39] Studies on chemerin and its relationship with PCOS are limited and controversial. For example, increased chemerin levels have been found in obese PCOS

patients with insulin resistance.[9,10,34,40] In addition, a positive relationship has been reported between increased chemerin levels and the regulatory activity of insulin[9] Fat mass is thought to be the major determinative factor for high chemerin values.[34] Serum chemerin was found to be significantly higher in hyperandrogenic PCOS patients compared with euandrogenic PCOS patients and controls and may be involved in the development of the metabolic syndrome in PCOS patients.[41] Nevertheless, one study reported no difference in chemerin levels when obese and normal weight PCOS patients were compared with healthy controls.[42] In the present study, there was no significant difference in circulating chemerin between PCOS patients and controls, but overweight PCOS patients had significantly higher levels of chemerin compared with normal weight PCOS patients. No significant difference was found between normal and overweight controls in serum chemerin. These current findings suggest that BMI alone is not a predictive factor for circulating chemerin. Studies have reported that in PCOS patients there is positive correlation between chemerin and BMI, triglyceride, HOMA-IR, LDL-C and an inverse correlation between chemerin and HDL-C.[10,41,42] In the present

study, a strong positive correlation was found between serum chemerin and BMI and a moderate positive correlation was found between serum chemerin and triglyceride, insulin, HOMA-IR and FAI in PCOS patients. A positive correlation between chemerin and BMI and triglyceride was also found in the control group. Multivariate regression analysis was used to identify independent predictors of chemerin in patients with PCOS and it used variables that were significantly correlated with chemerin levels. However, insulin, HDL-C and triglyceride were not used because they are strongly or moderately correlated with BMI, but mild correlations between BMI, HOMA-IR, and FAI were ignored. The present study identified the most predictive variables for circulating chemerin to be BMI, FAI and age.

A positive correlation was observed between chemerin and FAI in the PCOS patients. The negative effect of chemerin on aromatase has been shown to decrease oestrogen synthesis and distort folliculogenesis.[43] Follicles less than 10 mm in diameter will secrete more androgen,[44] which may explain why a positive relationship between chemerin and FAI was observed in the present study.

A limitation of the present study was the relative small sample size of overweight and normal weight PCOS patients. Although many patients were initially screened for the study, several did not provide informed consent. Further studies with larger sample sizes are required to confirm the current findings. In addition, this present study did not include obese patients or patients with insulin resistance, which may explain the lack of any difference between groups in omentin-1 concentrations.

In conclusion, the present study showed no difference in serum vaspin, omentin-1 and chemerin between PCOS patients and healthy controls. However, circulating chemerin was increased in overweight PCOS

patients compared with normal weight PCOS patients. The most predictive variables for circulating chemerin levels in PCOS patients were BMI, FAI and age. The present study also demonstrated significant increases in total cholesterol, LDL-C, total testosterone, free testosterone and FAI levels in PCOS patients compared with healthy controls, which support the suggestion that there is a relationship between metabolic syndrome components (e.g. dyslipidaemia) and androgen disorders in PCOS patients.[3] We postulate that chemerin may be one of the early markers in the development of metabolic syndrome and monitoring its levels may assist in the management of PCOS patients, particularly with regard to life style changes and diet in overweight patients.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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