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Comparative Evaluation of Serum METRNL and CTRP3 Levels in Women with Polycystic Ovary Syndrome

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Abstract

Meteorin-like protein (METRNL) and C1q/tumor necrosis factor-related protein 3 (CTRP3) are two fat tissue-related signal proteins which play a role in regulating the body's metabolism. Serum levels from METRNL and CTRP3 in women with polycystic ovary syndrome (PCOS) have been an area from study because of their potential relevance to both understanding the biology of PCOS as well as clinical implications. Purpose: To assess serum concentrations of METRNL and CTRP3 in PCOS-affected women compared to those without PCOS, and to evaluate several related metabolic and hemorheologic variables. This case-control study was conducted from May to September of 2026. The study participants consisted of 34 women with PCOS and 34 age-matched healthy control subjects who were recruited from laboratory facilities in Baghdad, Iraq. A physician diagnosed PCOS after evaluating each patient's clinical presentation, as well as her hormone profile; this included assessing her total testosterone, free testosterone, sex hormone binding globulin (SHBG), luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin (PRL) levels. In addition to hormone levels, the study evaluated participants' serum METRNL and CTRP3 levels, ages, BMI, HOMA-IR values, blood viscosities, and hematocrit percentages. To compare data between groups, researchers utilized appropriate statistical tests and adjusted for multiple comparisons using Holm's method. Spearman correlations and receiver operating characteristics (ROC) curves were generated to further explore possible relationships among variables. Serum METRNL and CTRP3 levels were found to be much lower in women who have PCOS than in control women (0.983 ± 0.188 vs. 1.858 ± 0.325 ng/mL and 1.841 ± 0.428 vs. 3.672 ± 0.605 ng/mL, respectively; both $P < 0.001$ after adjustment). Women with PCOS had considerably greater BMI, HOMA-IR, and blood viscosity than control women. However, hematocrit was not found to be significantly different. METRNL and CTRP3 did not correlate with HOMA-IR. There appeared to be a negative relationship between HOMA-IR and hematocrit. Women with PCOS in this cohort showed a decrease in circulating levels of METRNL and CTRP3. The results of this study suggest that these two adipokines should be studied more to see if they are part of the biochemical phenotype associated with PCOS. The correlations found through exploratory analyses and discriminatory estimations based on samples will need to be verified using larger, independently characterized cohorts.

Keywords

Polycystic ovary syndrome;
METRNL;
CTRP3.

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Introduction

Polycystic ovary syndrome (PCOS) is a complex, varied endocrine disorder characterized by abnormal reproductive function and often includes metabolic problems and changes in adipose tissue signals, because there are such wide variations in the clinical and metabolic symptoms that women with PCOS experience, it is important to evaluate metabolic characteristics along with reproductive dysfunction (Teede et al., 2023; Stener-Victorin et al., 2024). Recent articles have also focused on how adiposity, hormonal abnormalities, insulin resistance and other circulating biochemical mediators contribute to the development of PCOS (Helvaci and Yildiz, 2025; Merza et al., 2025). As a result, many researchers are now studying circulating adipokines as possible indicators of metabolic and inflammatory dysfunctions in women with PCOS.

Meteorin-like protein (METRNL), or subfatin, is a myokine and adipokine that regulates both metabolic functions and immune responses (Li et al., 2023). Studies on the concentration of METRNL in the blood of women with PCOS have produced conflicting results, for example, Fouani et al. (2020) found that women with PCOS had lower concentrations of METRNL in their blood than healthy women; however, Kabakchieva et al. (2024) and Paczkowska et al. (2024) did not find any difference in METRNL concentrations between the two groups. Majeed et al. (2024) studied METRNL concentrations in relation to obesity and other metabolic parameters in women with PCOS, these studies illustrate the inconsistency in METRNL concentrations and emphasize the need for additional studies of the function of METRNL in PCOS.

C1q/tumor necrosis factor-related protein 3 (CTRP3), as well as cartonectin, is an adipokine which is a part of glucose metabolism, insulin sensitivity, and inflammatory regulation, there is a growing body of evidence indicating that changes in circulating CTRP3 levels could potentially lead to metabolic abnormalities that are associated with PCOS, Zhao et al. (2023) showed that women with PCOS and insulin resistance had significantly reduced CTRP3 concentrations than women with PCOS who did not have insulin resistance. This indicates the metabolic role that CTRP3 may play in women with PCOS, additionally, Yu et al. (2023) found that CTRP3 has anti-inflammatory properties by using the SIRT1/NF-κB signaling pathway in experimental models of intestinal inflammation. Also, Barbieri et al. (2023) studied circulating CTRP3 with respect to obesity and chronic kidney disease progression, indicating a wide range of studies being done on its metabolic and clinical implications.

The systematic and narrative reviews that document a wide range of circulating adipokine concentration and the relationship between insulin resistance and other metabolic issues highlight the complexity of how adipokines are regulated in PCOS (Kruszewska et al., 2022; Walford et al., 2024). While there is an increasing amount of research on these proteins, the available data on METRNL and CTRP3 remains conflicting, and the circulating levels of both have not been consistently compared among various PCOS populations.

Evaluating both proteins simultaneously in the same study population would allow for more comprehensive assessment of adipokine changes related to PCOS than assuming that the circulating levels of both proteins always reflect the extent of insulin resistance. Therefore, the aimed from this study was to compare serum METRNL and CTRP3 concentrations in female with PCOS versus healthy control women from Baghdad, Iraq; as well as to determine if there are relationships among serum METRNL/CTRP3 concentration, BMI, HOMA-IR, blood viscosity, and hematocrit.

Materials and Methods

A laboratory-based case–control study, this research took place in Baghdad, Iraq, from May through September 2026. This study included a total of 68 female subjects, including 34 females who had been diagnosed with Polycystic Ovary Syndrome (PCOS) and 34 females who did not have PCOS. All participants in this study were identified and recruited via outside medical laboratories located in Baghdad. The diagnosis of PCOS was confirmed by a

specialist physician before blood samples were collected, through clinical evaluation and routine hormonal assessment. A complete diagnostic evaluation was completed using total testosterone, free testosterone, sex hormone binding globulin (SHBG), luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin (PRL). Hormonal testing is part of routine clinical assessment and therefore is not listed as one of the biochemical variables assessed in this study. The primary study biomarkers evaluated following clinical classification were serum METRNL and CTRP3 concentrations. Other variables measured included age, BMI, HOMA-IR, whole blood viscosity and hematocrit

Biochemical and hematological measurements

Commercial human enzyme-linked immunosorbent assay (ELISA) kits were used to detect the serum levels of METRNL and CTRP3 (BT LAB, China; Catalog Numbers E3941Hu and E3300Hu, respectively), as instructed by the manufacturer. Both markers were reported in (ng/mL). For every person who participated, age and body mass index (BMI, kg/m2) were documented. To assess insulin resistance, the homeostatic model assessment from insulin resistance (HOMA-IR) was used based on fasting glucose and insulin levels. The collection of whole blood into EDTA-containing tubes was performed to allow for the measurement of hemorheological parameters (blood viscosity). The Brookfield DV2T Cone/Plate Viscometer (AMETEK Brookfield, USA) was used to measure blood viscosity using a rotational cone-and-plate system. Viscosity data were reported in mPa·s. Hematocrit values were obtained as a percentage (%) and used in the comparison of women with PCOS versus healthy control subjects.

Statistical analysis

Data is symbolized as mean ± standard deviation (SD). Shapiro-Wilk test was utilized to determine whether the data followed a normal distribution. According to the kind of data, either the Mann-Whitney U test or Welch's t-test, were utilized to compared. Spearman correlation analysis was utilized to analyze relationships among different variables in women with PCOS. Multiple comparisons were adjusted for using Holm method. ROC curves were created to evaluate the exploratory diagnostic accuracy from the measured variables. statistical significance was defined as an adjusted P-value of less than 0.05 on both sides.

Results

The average age was similar for the two groups of subjects; however, BMI was significantly greater for the PCOS group. Both METRNL and CTRP3 were found to be at lower levels in the sera of the women who had PCOS when compared to the healthy control group, even after adjusting for multiple comparisons using Holm's method ($P<0.001$). On the other hand, the PCOS group had considerably greater HOMA-IR and whole blood viscosity ($P<0.001$), however there was no significant change in hematocrit among the two groups (Table 1).

Table 1. Clinical and laboratory features in PCOS-affected and control women.

Variable	Controls (n=34)	PCOS (n=34)	P	Holm P
Age (years)	29.353 ± 4.396	27.971 ± 4.482	0.204	0.407
BMI (kg/m²)	24.856 ± 2.811	28.974 ± 2.722	<0.001	<0.001
METRNL (ng/mL)	1.858 ± 0.325	0.983 ± 0.188	<0.001	<0.001
CTRP3 (ng/mL)	3.672 ± 0.605	1.841 ± 0.428	<0.001	<0.001
HOMA-IR	1.851 ± 0.541	4.378 ± 0.782	<0.001	<0.001
Blood viscosity (mPa·s)	4.627 ± 0.520	5.287 ± 0.517	<0.001	<0.001
Hematocrit (%)	39.966 ± 2.063	39.795 ± 1.234	0.577	0.577

In the PCOS group there was a slight negative relationship between METRNL and HOMA-IR and no relationship between CTRP3 and HOMA-IR; both were not statistically significant. There was a moderate positive relationship between METRNL and CTRP3 nevertheless, this relationship did not reach statistical significance when the Holm correction was applied. However, after adjustments were made, HOMA-IR had a significantly negative relationship with hematocrit (Spearman ρ = −0.581, adjusted P = 0.0067), as seen in Table 2.

Table 2. Spearman correlations within PCOS cases.

Variable pair	Spearman ρ	Unadjusted P	Holm P
Age – BMI	+0.273	0.118	1.000
Age – METRNL	+0.111	0.534	1.000
Age – CTRP3	+0.128	0.472	1.000
Age – HOMA-IR	-0.214	0.224	1.000
Age – Blood viscosity	-0.064	0.718	1.000
Age – Hematocrit	+0.387	0.024	0.449
BMI – METRNL	+0.093	0.600	1.000
BMI – CTRP3	+0.286	0.101	1.000
BMI – HOMA-IR	+0.162	0.361	1.000
BMI – Blood viscosity	-0.113	0.526	1.000
BMI – Hematocrit	-0.045	0.801	1.000
METRNL – CTRP3	+0.421	0.013	0.263
METRNL – HOMA-IR	-0.259	0.139	1.000
METRNL – Blood viscosity	-0.183	0.300	1.000
METRNL – Hematocrit	+0.103	0.562	1.000
CTRP3 – HOMA-IR	+0.049	0.784	1.000
CTRP3 – Blood viscosity	-0.115	0.516	1.000
CTRP3 – Hematocrit	+0.190	0.281	1.000
HOMA-IR – Blood viscosity	+0.355	0.040	0.712
HOMA-IR – Hematocrit	-0.581	<0.001	0.007
Blood viscosity – Hematocrit	+0.017	0.922	1.000

The ROC curves for METRNL and CTRP3 demonstrated very high discriminative ability in distinguishing between women who have PCOS and healthy women. Specifically, the area under the curve (AUC) value for METRNL was 0.988, while that for CTRP3 was 0.992. Using the cutoff value for METRNL of ≤1.290 ng/mL, the sensitivity was 100%, and the specificity was 97.1%. For CTRP3, using the cutoff value of ≤2.481 ng/mL, the sensitivity was 97.1%, and the specificity was 94.1%. HOMA-IR was able to discriminate well (AUC = 0.997), and BMI and blood viscosity were able to discriminate moderately well (AUC = 0.846 and 0.835, respectively). Conversely, hematocrit and age were not able to discriminate well (AUC = 0.540 and 0.579, respectively). This demonstrates the significant discriminatory ability of METRNL and CTRP3 in the population studied (Table 3).

Table 3. Exploratory ROC statistics.

Variable	AUC	Youden cutoff	Sensitivity	Specificity
METRNL (ng/mL)	0.988	≤1.290	100.0%	97.1%
CTRP3 (ng/mL)	0.992	≤2.481	97.1%	94.1%
HOMA-IR	0.997	≥3.230	100.0%	97.1%
BMI (kg/m²)	0.846	≥26.700	82.4%	73.5%
Blood viscosity (mPa·s)	0.835	≥5.286	64.7%	91.2%
Hematocrit (%)	0.540	≤40.840	85.3%	38.2%
Age (years)	0.579	≤29.000	64.7%	47.1%

Discussion

This study established that PCOS-affected women had significantly lower levels from serum METRNL and CTRP3, indicating a possible alteration in how these two adipokines are regulated as part of the syndrome, this data further supports the exploration of these two proteins as circulating biomarkers for PCOS, the decrease in METRNL levels was consistent with what was found in Fouani et al. (2020) work which showed reduced blood-borne concentrations of METRNL in female with PCOS.

Conversely, both Kabakchieva et al. (2024) and Paczkowska et al. (2024) did not find any difference in METRNL levels among patients and controls, Majeed et al. (2024) evaluated the relationship of METRNL with weight status, these conflicting results could be due to differences in metabolic phenotype, degree of adiposity, and methodological approaches used in each study, moreover, the various metabolic and immunoregulatory functions of METRNL as discussed by Li et al. (2023) also support the idea that METRNL may play a role in PCOS.

The lower concentration from CTRP3 in the blood is similar to what was found by Zhao et al. (2023) as they showed that insulin-resistant PCOS-affected women levels were decreased of CTRP3 than women with PCOS but not insulin-resistant, in addition to being able to help regulate metabolism, the anti-inflammatory effects from CTRP3 that were demonstrated in experiments (Yu et al., 2023) provide a biological rationale for how it may play a role in metabolic diseases.

Additionally, Kruszewska et al. (2022) and Walford et al. (2024) described how complex the regulation of adipokines is and this provides further support for studying CTRP3 in PCOS, while METRNL and CTRP3 were variance among PCOS-affected women and control subjects, neither correlated with HOMA-IR in women with PCOS, therefore, changes in circulating levels of adipokines do not appear to be representative of individual differences in insulin resistance, women with PCOS have diverse metabolic profiles due to variations in adiposity and hormonal abnormalities that could explain why there were no correlations observed (Bril et al., 2024; Helvaci and Yildiz, 2025; Stener-Victorin et al., 2024).

Additionally, several other studies have demonstrated how complexly regulated insulin resistance is in women with PCOS (Chen et al., 2025; Kisiała et al., 2026; Wang et al., 2022; Tilak et al., 2022). An increase in blood viscosity is another piece of evidence indicating that there are hemorheological changes occurring in women who suffer from PCOS, this finding is similar to those reported by Simmonds et al. (2016), the negative relationship found between HOMA-IR and hematocrit was an exploratory finding, which could indicate the presence of complicated relationships between metabolism and hematology, however, because of the small sample size used in the present study and possible other factors that were

not accounted for, further research on larger studies will be needed to confirm this relationship, the higher than expected ROC AUC values for METRNL and CTRP3 indicate a strong ability of both to discriminate within the cohort, however, it will be important to validate these results with other independent cohorts to assess whether they are applicable to a larger population, as is common practice when developing biomarkers.

Conclusion

In this study, there was a statistically significant decrease in both serum METRNL and CTRP3 concentrations in women with PCOS when compared to the healthy control population. This finding suggests that these two adipokines may be useful as potential serum biomarkers for the identification of PCOS. While neither of these two adipokines demonstrated a statistically significant correlation with HOMA-IR in the PCOS population, the results suggest that there should be continued exploration of the possible physiological roles of these two adipokines. It would also be beneficial to conduct larger studies with more extensive clinical characterization and independent validation to determine if they could serve as potential biomarkers for PCOS.

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