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# Circulating levels of irisin and Meteorin-like protein in PCOS and its correlation with metabolic parameters

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## Abstract

**Introduction:** Research on obesity, which results from excessive food consumption and sedentary lifestyle, has focused on increasing energy expenditure. Recently, muscle tissue is being investigated as an endocrine active organ, secreting molecules called myokines. Multiple studies have been performed to assess myokine levels in various disorders, including polycystic ovary syndrome (PCOS) and metabolic syndrome. Irisin and Meteorin-like protein (Metrnl) are particles which, among others, are suggested to play an important role in adipose tissue browning and improving insulin sensitivity.

**Material and methods:** The study population consisted of 31 women with PCOS and 18 healthy individuals. PCOS was diagnosed based on revised 2003 Rotterdam criteria. Multiple anthropometrical, hormonal, and biochemical parameters were assessed, including oral glucose tolerance test and body composition with dual energy X-ray absorptiometry. Serum levels of irisin and Metrnl were measured by enzyme-linked immunosorbent assay (ELISA).

**Results:** There were no differences between the PCOS and control groups according to age, body mass index (BMI), waist-to-hip ratio (WHR), fasting glucose, homeostasis model assessment of insulin resistance (HOMA-IR), or body mass composition. Assessment of Metrnl and irisin concentrations revealed no significant differences between PCOS and healthy women. The irisin level was negatively correlated with BMI, body fat mass, fasting glucose, and insulin concentrations. No relationship between Metrnl level and metabolic parameters was found.

**Conclusions:** Although irisin seems to be a promising biomarker, inconsistent research limits its value in clinical use in the assessment or treatment of obesity. Metrnl level was not affected in the study population, but it might be connected to the severity of metabolic disturbances. **(Endokrynol Pol 2024; 75 (2): 199–206)**

**Key words:** *irisin; Meteorin-like protein; Metrnl; myokines; metabolic disturbances; obesity; PCOS*

## Introduction

The global prevalence of obesity has nearly tripled during the past 4 decades, and this trend has been observed in different regions worldwide [1]. As a result, between 1990 and 2015 an increase in deaths and disability rates related to overweight and obesity was estimated of approximately 28% and 35%, respectively [2]. Obesity is associated with numerous health issues, including diabetes mellitus, cardiovascular disease, sleep apnoea, depression, and bone metabolism disturbances [3, 4], which are related to changes in adipose metabolism [5]. It was found that among overweight and obese women, approximately a quarter of them suffer from polycystic ovary syndrome (PCOS) [6].

PCOS is one of the most common endocrinopathies among reproductive-age women [7]. Clinical presentation varies between patients; however, reproductive, dermatological, metabolic, and psychological issues may be present [8]. Polycystic ovary syndrome, as a condition affecting women's metabolic health from young age, might be a biological model of insulin resistance and early metabolic disturbances.

In the past, skeletal muscle function was thought to be mainly associated with locomotion and body posture. Recently, studies revealed that myofibers, in response to exercise, express and release different factors that have paracrine and endocrine effects [9]. This group of molecules, called "myokines", includes irisin and Meteorin-like protein (Metrnl). Research on obesity, resulting from excessive food consumption and sedentary lifestyle, has focused on increasing energy expenditure, and muscle tissue is being investigated as an endocrine active organ.

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Irisin was firstly described by Boström et al. in 2012. It is a product of the proteolytic cleavage of fibronectin type III domain containing 5 (FNDC5) by as-yet-unknown enzymes. [10]. It was revealed that FNDC5 expression was higher in muscles and organs composed of muscles, such as the tongue, rectum, or heart and was significantly lower in the adipose tissue [11].

Irisin was found to be involved in various metabolic pathways; it also has an influence on glucose metabolism in skeletal muscle cells through the AMPK pathway [12], induces the translocation of GLUT4 to the cell membrane, stimulates glucose uptake [13], and downregulates the expression of genes involved in gluconeogenesis and glycogenolysis. [14] Moreover, a positive influence of irisin on the nervous system was suggested, and this myokine is suspected to be an important particle in exercise-induced neuroprotection [15, 16]. One of the main possible roles of irisin is promoting energy expenditure through influencing the differentiation of white adipose tissue (WAT) into brown adipose tissue (BAT) [17]. Circulating irisin concentration has a day-night secretion rhythm [18] and increases shortly after acute exercise [14]; however, no statistical differences were reported in regard to irisin levels between people with low, moderate, or high physical activity [18]. Additionally, it was reported that the irisin level is not related to dietary habits and does not change after meal consumption [18].

Expression in various tissues and circulating levels of irisin have been investigated in numerous disorders, including obesity, diabetes mellitus, neuropsychiatric disorders, and cancers. Circulating levels of irisin tend to be decreased in several types of cancer [19]; however, higher expression of irisin in breast cancer tissue was reported as a good prognostic marker [20]. Although the results from studies related to metabolic disorders are inconclusive, some research suggests higher concentrations of irisin in individuals with obesity or DM, and this phenomenon was explained as possible "irisin resistance" [21].

Metrnl, also called subfatin, is a particle with approximately 40% similarity to Meteorin, according to amino acid sequence [22], but the physiological functions of those proteins differ. Meteorin is a factor that plays a role in neurogenesis [23], while Metrnl was suggested to be involved in maintaining metabolic homeostasis [24]. Expression of Metrnl was found in various organs, including liver, spleen, heart, skin, fat, and muscle tissue [25]. Similarly to Irisin, the expression of Metrnl in adipose and muscle tissue is enhanced by physical exercise and exposure to cold. Moreover, there is evidence linking Metrnl with an improvement in insulin sensitivity, an increase in energy expenditure, and positive regulation of thermogenic gene expression associated with promoting browning of adipose tissue. Moreover, an anti-inflammatory function of Metrnl was reported [26]. In the muscle tissue, Metrnl improves insulin sensitivity through AMP-activated protein kinase (AMPK) or peroxisome proliferator-activated receptor (PPAR ) [27]. On the other hand, it was suggested that Metrnl concentration is altered in several disorders, including obesity, diabetes mellitus type 2, and cardiovascular disease [28–30]. Additionally, Metrnl has been investigated as a diagnostic biomarker or therapeutical target in cardiometabolic disorders [31].

The aim of the study was to assess circulating levels of irisin and Metrnl, 2 myokines with potentially similar physiological functions, in women with PCOS in relation to severity of metabolic disturbances.

## Material and methods

### *Description of the study population*

The study population included 49 Caucasian women: 31 with PCOS and 18 healthy individuals. PCOS was diagnosed based on the revised 2003 Rotterdam criteria after excluding related disorders [32]. Among inclusion criteria for whole study population were as follows: age between 18 and 40 years, no history of hypoglycaemic or hypolipidaemic treatment, and not using hormonal contraception for at least 6 months prior to tests. Exclusion criteria were as follows: pregnancy, diabetes mellitus (DM), history of bariatric surgery, chronic disease with therapy that has an influence on hormonal secretion, loss of 10% or more body weight in the 3 months prior to the tests. Besides those mentioned above, an additional criterion for the control group was no history of menstrual irregularity in the past 3 years. Patients were asked to perform their usual daily physical activity for the 7 days prior to tests.

The research was conducted under the Declaration of Helsinki, and approval was obtained from the Ethical Committee of Wroclaw University of Medical Sciences (approval no KB-566/2020). All individuals who participated in the study provided written consent.

### *Anthropometrical parameters*

Weight, height, and waist and hip circumferences were measured with standard techniques. Body mass index (BMI) was calculated with the formula:

$$BMI = weight\ [kg]/height^2\ [m^2].$$

Overweight was defined as BMI ≥ 25, and obesity was diagnosed in patients with BMI equal to or higher than 30, in accordance with World Health Organisation (WHO) criteria [33]. Taking into consideration the BMI criterion, the study population was divided into 2 groups: normal-weight (NW) or overweight/obese (OW).

Waist circumference (WC) greater than or equal to 80 cm was a criterium to define central obesity. Consequently, the group of women with abdominal obesity (AbO+) was separated from the study population.

### *Hormonal and biochemical assessment*

All participants were examined, and all tests were performed in follicular phase, between the third and sixth day of the menstrual cycle. Blood samples were taken after overnight fasting; biochemical and hormonal assessments were performed with commercially available methods.

An oral glucose tolerance test with 75 g of glucose was performed, and glucose and insulin levels were measured before the test,

and after 60 and 120 minutes. Homeostatic model assessment of insulin resistance (HOMA-IR) was used to assess insulin resistance, and HOMA IR was calculated with the standard formula:

$$HOMA\text{-}IR = insulin\ (\mu U/mL) \times glucose\ (mmol/L)/22.5.$$

Insulin resistance was defined as HOMA-IR higher than 2.5 [34–36].

### *Body composition*

Body composition was assessed with dual-energy X-ray absorptiometry (DXA). Hologic Discovery QDR Series densitometer (Hologic Incorp. USA, APEX 4.5.2.1, Windows 7 Professional system) was used for the measurements.

### *Irisin and Metrnl levels*

Concentrations of serum irisin and Metrnl were measured in duplicate by ELISA using commercially available assays. The following kits were used: Irisin ELISA Kit (BioVendor, Czech Republlic, Catalogue No. RAG018R; sensitivity 1.0 ng/ml) and Human Meteorin-like protein (METRNL) ELISA Kit (Assay Genie, Ireland, Catalogue No. HUEB2525; sensitivity 7.3 pg/ml). Assays were carried out according to the manufacturers' protocols.

### *Statistical analysis*

Statistical analyses were performed with Statistica (TIBCO), version 13.3. The T-test and the Mann-Whitney U test were used to compare anthropometrical, biochemical, and hormonal parameters with irisin and Metrnl levels for normally and non-normally dispersed data, respectively. The correlations between parameters were assessed with Spearman correlation. In all analyses a p-value less than 0.05 was considered as statistically significant.

## Results

Comparison of basic anthropometrical, biochemical, and hormonal parameters between the PCOS and control groups is shown in Table 1. There were no differences in terms of age, BMI, WHR, fasting glucose, HOMA-IR, or body mass composition. In the study population PCOS women had significantly higher LH/FSH ratio and lower waist circumference.

Statistical analysis revealed no significant differences in Metrnl or irisin levels between PCOS and healthy individuals as shown in Figures 1 and 2. However, irisin concentrations were in the narrow range of higher values.

The study population was divided into 2 groups: normal-weight and overweight or obese patients. The Metrnl level did not differ between those groups, as shown in Figure 3. Conversely, irisin concentrations differed between groups and were significantly higher in normal-weight women (Fig. 4).

Correlations between irisin and Metrnl levels and other parameters are presented in Table 2.

The irisin level was negatively correlated with BMI, body fat mass, android-to-gynoid ratio, and fasting glucose and positively correlated with HDL. There were

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**Table 1.** ***Comparison of anthropometric, biochemical, and hormonal parameters between polycystic ovary syndrome (PCOS) and control group***

| Parameter | PCOS | Control | p-value |
|---|---|---|---|
| Age [years] | 26.0 ± 3.6 | 28.0 ± 5.6 | 0.14 |
| BMI [kg/m$^2$] | 26.17 ± 7.41 | 28.92 ± 7.10 | 0.23 |
| Waist circumference [cm] | 82.0 ± 15.6 | 93.9 ± 16.7 | 0.04 |
| WHR | 0.80 ± 0.08 | 0.83 ± 0.06 | 0.24 |
| Fasting glucose [mg/dL] | 84.5 ± 8.0 | 86.1 ± 7.0 | 0.49 |
| HOMA-IR | 2.02 ± 1.63 | 2.50 ± 2.1 | 0.42 |
| Body fat mass [kg] | 26.74 ± 11.52 | 32.88 ± 12.23 | 0.13 |
| Body lean mass [kg] | 46.73 ± 10.4 | 49.98 ± 10.84 | 0.36 |
| TCh [mmol/L] | 4.54 ± 0.83 | 4.26 ± 1.29 | 0.65 |
| HDL [mmol/L] | 1.35 ± 2.07 | 1.36 ± 0.53 | 0.88 |
| LDL [mmol/L] | 2.62 ± 0.88 | 2.46 ± 0.88 | 0.85 |
| TG [mmol/L] | 0.95 ± 0.49 | 0.96 ± 0.74 | 0.58 |
| TSH [$\mu$IU/mL] | 1.50 ± 1.18 | 1.58 ± 0.67 | 0.82 |
| LH/FSH | 1.42 ± 0.76 | 0.77 ± 0.35 | 0.002 |
| Oestradiol [pg/mL] | 49.59 ± 38.35 | 39.64 ± 16.43 | 0.34 |
| Testosterone [ng/mL] | 0.38 ± 0.16 | 0.32 ± 0.12 | 0.25 |
| Androstenedione [ng/mL] | 3.37 ± 1.37 | 2.94 ± 2.15 | 0.41 |
| SHBG [nmol/L] | 50.17 ± 26.19 | 44.96 ± 24.03 | 0.56 |

BMI — body mass index; WHR — waist-to-hip ratio; HOMA-IR — homeostasis model assessment of insulin resistance; TCh — total cholesterol; HDL — high-density lipoprotein; LDL — low-density lipoprotein; TG — triglycerides; TSH — thyroid-stimulating hormone; LH — luteinising hormone; FSH — follicle-stimulating hormone; SHBG — sex hormone-binding globulin

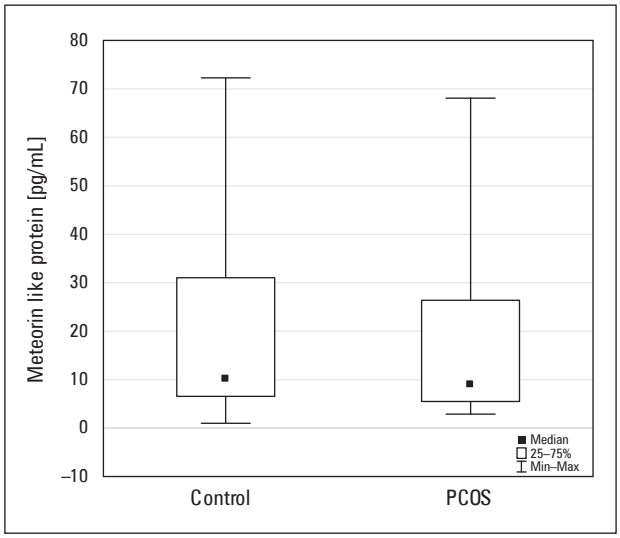


**Figure 1.** *Comparison of circulating Meteorin-like protein (Metrnl) level between polycystic ovary syndrome (PCOS) women and control group*

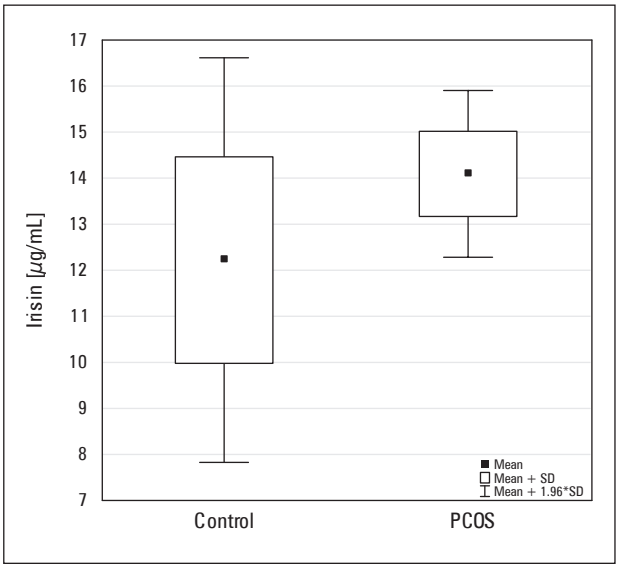


**Figure 2.** *Comparison of circulating irisin levels between polycystic ovary syndrome (PCOS) women and control group*

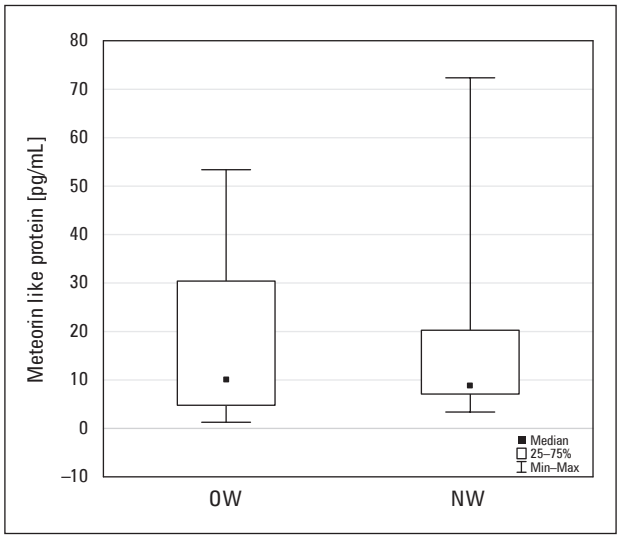


**Figure 3.** *Comparison of circulating Meteorin-like protein (Metrnl) levels between women with body mass index (BMI) equal or greater than 25 (OW) and normal-weight individuals (NW); p = 0.77*

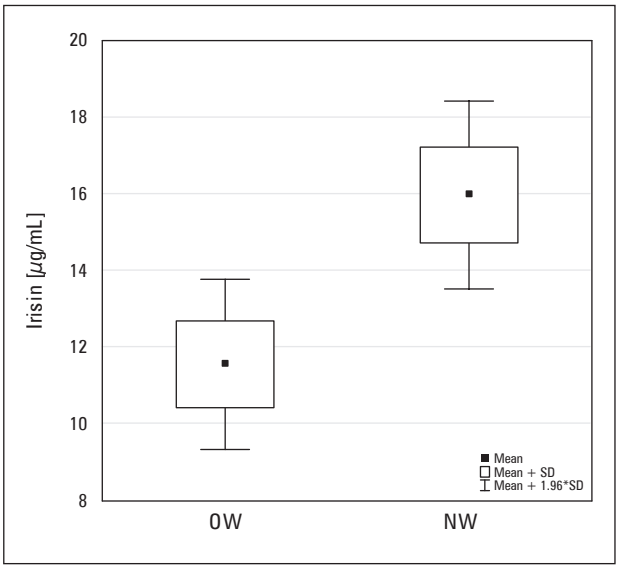


**Figure 4.** *Comparison of circulating irisin levels between overweight or obese women (OW) and normal-weight individuals (NW); p < 0.05*

no significant relationships between LH/FSH ratio, testosterone, or androstenedione and irisin concentrations.

The Metrnl concentration was not significantly associated with anthropometrical and biochemical parameters; the only correlation was a positive one with androstenedione level.

## Discussion

In the current study, irisin and Meteorin-like protein, 2 myokines engaged in regulation of energy metabolism, were measured in a PCOS population in comparison to healthy individuals. The myokines level was assessed with reference to various parameters, including body composition, to better understand influencing factors.

Analysis of irisin showed significantly higher concentrations in normal-weight women when compared to the group of overweight and obese individuals. Moreover, there were negative correlations between irisin level and BMI, fat mass, and the proportion between fat mass and whole body mass. A negative relationship was also found between circulating irisin

**Table 2.** *Correlation coefficients between circulating irisin and Meteorin-like protein (Metrnl) levels and anthropometrical, biochemical, and hormonal parameters*

| | Irisin | Metrnl |
|---|---|---|
| BMI | –0.538* | 0.208 |
| Androstenedione | –0.219 | 0.341* |
| Testosterone | –0.209 | 0.122 |
| LH/FSH | 0.059 | 0.27 |
| Trunk fat mass | –0.567* | 0.212 |
| Whole body fat mass | –0.592* | 0.200 |
| Android/gynoid ratio | –0.428* | 0.102 |
| Trunk/limb fat mass ratio | –0.443* | 0.154 |
| Whole body fat/whole body mass | –0.444* | 0.231 |
| HOMA–IR | –0.580* | –0.093 |
| Fasting glucose | –0.492* | 0.169 |
| Total cholesterol | –0.073 | –0.071 |
| HDL | 0.445* | –0.057 |
| Triglycerides | –0.204 | –0.162 |
| Irisin | | –0.115 |

BMI — body mass index; LH — luteinising hormone; FSH — follicle-stimulating hormone; HOMA-IR — homeostatic model assessment of insulin resistance; HDL — high-density lipoprotein; *$p < 0.05$

and markers of carbohydrate metabolism: fasting glucose and HOMA-IR.

Literature data regarding a link between patients' BMI and irisin concentrations are inconclusive. There are studies suggesting positive, negative, as well as no correlation between those parameters; however, more studies reported higher irisin levels in individuals with higher BMI [37]. At the same time, comparison of OW women to NW individuals in the PCOS population showed significantly higher irisin levels in the first group [38].

On the other hand, elevated levels of irisin in obese population were reported to be connected with lower risk of complications related to cardiometabolic disease [39]. It was also suggested that increased irisin concentration might improve insulin sensitivity and is connected to lower risk of insulin resistance [40]. PCOS is strongly associated with altered glucose metabolism and insulin secretion, and the coexistence of both factors in our study population, obesity and insulin resistance, might have an impact on irisin level.

Results from the present study did not show significant differences in irisin levels between the PCOS and control groups. Moreover, irisin and androgen concentrations were not correlated.

Literature data regarding irisin levels in PCOS are conflicting: higher, lower, and comparable concentrations were reported in the PCOS group when compared to the control group [41–45]. A meta-analysis summarising 8 studies suggested increased circulating irisin level in PCOS patients; however, differences were not seen when PCOS women were compared to BMI-matched healthy controls [46]. Results from our study are in agreement with this conclusion [46]; there were no differences in circulating irisin, but the PCOS and control groups were similar according to BMI and other anthropometrical parameters, including WHR and total fat mass, but not for WC. Comparable irisin concentrations between the study and control groups suggest an alteration of irisin level as a result of metabolic disturbances accompanying PCOS.

Research assessing the relationship between circulating androgens and irisin levels is limited, and the results are contradictory. On the one hand, it was reported that increased FAI corresponded with higher irisin levels, and FAI was assessed as the main prognostic factor of an elevated irisin level [47]; on the other hand, a negative correlation between circulating irisin level and LH, testosterone, and FAI was also presented in adolescents and adults with PCOS [43, 48], or no relationship was found in adult PCOS women [45].

An inconsistency between research regarding hyperandrogenaemia and irisin concentration might be partially caused by physiological connection of hyperandrogenaemia to insulin resistance. Increased levels of insulin enhance secretion of ovarian androgens [49] and inhibit the production of sex hormone-binding globulin [50]; what is more, androgen excess is correlated with the reduction of insulin sensitivity in skeletal muscles [51]. Our results did not show any relationship between androgen and irisin levels; however, significant correlation with the surrogate marker of insulin resistance was present.

In the current study there were no differences in Metrnl concentrations between women with and without PCOS or between normal-weight and obese or overweight individuals. Additionally, we found a correlation only between Metrnl and androstenedione level; there were no statistically significant relationships between Metrnl level and other hormonal, biochemical, or anthropometrical parameters.

As far as we know, Metrnl levels were analysed in PCOS only in 2 independent studies [52, 53]. In both studies significantly lower Metrnl levels were found in PCOS women when compared to healthy controls. In the first study, PCOS patients were divided into 2 groups: infertile patients and patients with recurrent pregnancy loss (RPL; defined as 2 or more losses of pregnancy before 20 weeks of gestation). Women with RPL have higher Metrnl serum levels when compared to infertile patients [52].

Inconsistency between our results and the data presented in the literature might be connected to dis-

similarities in study design as well as to differences in the study population. In contrast to the first study [52], infertility or RPL were not an inclusion criterion for PCOS women in our study. Additionally, individuals who participated in our research did not take medicaments influencing glucose metabolism. In both the studies mentioned above, PCOS women had more strongly expressed insulin resistance, and a negative correlation between Metrnl and HOMA-IR was found [52, 53]. In the second study, the association between Metrnl and HOMA-IR was only observed in PCOS, not in the control group [53]. In our study, the PCOS women had insignificantly lower BMI and HOMA-IR when compared to controls. The differences in metabolic parameters between individuals participating in the studies might be related to the observed inconsistency in Metrnl levels in PCOS.

Existing findings regarding relationships between Metrnl concentrations and anthropometrical or biochemical parameters are inconclusive. Higher Metrnl expression was found in adipose tissue of obese children in comparison to lean individuals [54]; however, the studies related to the circulating level of Metrnl as a biomarker of obesity are inconsistent. Some research reported higher levels of Metrnl in overweight or obese patients when compared to a normal-weight population [55, 56], but conversely lower levels of Metrnl [57, 58] or no significant differences were also shown [52, 59]. At the same time, variations in circulating Metrnl were observed according to the presence of additional comorbidities, such as DM; higher levels of Metrnl in a diabetic population were not found in a non-diabetic group [56].

Moreover, studies are contradictory in terms of the relationship between circulating Metrnl level and metabolic parameters such as BMI, waist circumference, percentage of fat tissue, or insulin sensitivity. Negative correlations between Metrnl concentration and HOMA-IR [57], BMI [58, 60], visceral fat area, and TG and TCh levels [58, 61] were reported. On the other hand, a positive association between circulating Metrnl and BMI, TCh, TG, or HOMA-IR [55] and no relationship between Metrnl level and BMI was also described [61].

Taking into consideration the results from the present study and the literature data mentioned above, changes in circulating Metrnl might be connected to the severity of the metabolic disorders and hence not observed in milder disturbances of carbohydrate metabolism. What is more, duration of metabolic disease and number of complications or additional health issues might have an impact as well.

To the best of our knowledge, this is the first study comparing circulating irisin and Metrnl in the PCOS population; our study did not show a significant correlation between those myokines in this group.

Correlation between irisin and Metrnl levels was observed in one study of a group of patients with DM2 in the male population; this association was not confirmed in non-diabetic individuals and the female population of the study [56]. What is more, in a study comparing diabetic to non-diabetic individuals, Metrnl and irisin concentrations were not correlated when assessed in the whole study population [55].

Bearing in mind the similar physiological functions of irisin and Metrnl, no correlation between circulating levels of those myokines suggests individual roles rather than synergetic actions in physiological adaptation to metabolic disease. It is possible that different regulatory factors trigger the secretion of both myokines, and, as a result, their concentrations are unevenly affected by metabolic disturbances.

The most important limitation of the study was a small size of the groups. However, the results presented in this paper are the first phase of the study; the research continues and we intend to provide more comprehensive data of larger groups in the close future.

## Conclusions

Although irisin seems to be a promising biomarker, inconsistent research limits its value in clinical use in the assessment or treatment of obesity. However, the correlation of irisin concentration with metabolic parameters suggests its important role in maintaining homeostasis. Metrnl level was not affected in the study population, but it might be connected to the severity of metabolic disturbances.

### *Data availability statement*

The data presented in this study are available on request from the corresponding author. The data are not publicly available.

### *Ethics statement*

The research was conducted under the Declaration of Helsinki and obtained approval from the Ethical Committee of Wroclaw University of Medical Sciences (approval no. KB-566/2020).

### *Author contributions*

Conceptualisation: K.P. and J.D.; methodology: K.P., A.Z., J.D.; validation: K.P. and J.D.; formal analysis: K.P., J.K., and J.D.; investigation: K.P., J.S., K.Z., D.J., A.Z.; resources: K.P., J.S., K.Z., D.J., D.K-W., and J.D.; data curation: K.P. and J.K.; writing—original draft preparation: K.P. and J.D.; writing—review and editing: K.P., J.D., D.J., A.Z., and M.B.; visualisation: K.P.; supervision: J.D.; project administration: K.P. and J.D.; funding acquisition: KP, JD, and MB. All authors have carefully read and accepted the manuscript.

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## *Conflict of interest*

The authors have no conflicts of interest to declare.

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