# Serum Metrnl Level is Correlated with Insulin Resistance, But Not with β-Cell Function in Type 2 Diabetics

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Metrnl is a novel identified adipomyokine which might have therapeutic potential for metabolic and inflammatory diseases, including type 2 diabetes mellitus. We aimed to explore the associations of circulating Metrnl level with β-cell function and insulin resistance (IR) and further explore the possible correlation between Metrnl and another adipomyokine named irisin in patients diagnosed type 2 diabetes.

Material/Methods: Our study recruited 59 participants with type 2 diabetes and 30 normal glucose tolerance (NGT) participants. We used enzyme-linked immunosorbent assay (ELISA) to measure serum levels of Metrnl and irisin. The associations of Metrnl level with indexes of β-cell function and IR and irisin level were analyzed by multiple linear regression analysis or spearman correlation analysis.

Results: Compared with NGT participants, serum Metrnl level was elevated in participants with type 2 diabetes: 210.30 pg/mL (range 105.94–323.91 pg/mL) versus 132.02 pg/mL (range 104.93–195.92 pg/mL). Metrnl level did not show significant correlation with β-cell function-related indicators, but positively correlated with HOMA2-IR and negatively correlated with HOMA2-%S after controlling multiple covariates in participants with type 2 diabetes. Metrnl level was also not associated with obesity-related indicators (body mass index, waist circumference, body fat percentage, and visceral adipose tissue area) in the type 2 diabetes group. In addition, the correlation between Metrnl and irisin level was also not present ($r$=–0.159, $P$=0.229) in type 2 diabetes group.

Conclusions: Serum Metrnl level was associated with IR, but not with β-cell function in participants with diagnosed type 2 diabetes.

MeSH Keywords: Cytokines • Diabetes Mellitus, Type 2 • Insulin Resistance • Insulin-Secreting Cells

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# Background

Islet β-cell dysfunction and insulin resistance (IR) are 2 leading causes of type 2 diabetes mellitus (T2DM) [1]. Regenerating pancreatic β-cell mass and improving IR are 2 crucial research directions for the treatment of T2DM [2,3]. The role of chronic systemic inflammation in the occurrence and development of β-cell dysfunction and IR had been demonstrated by many recent discoveries; T2DM has also been regarded as an inflammatory disease [4].

Recently, a novel secreted adipomyokine named Metrnl was discovered, and it can be induced by exercise (in muscle) or upon cold exposure (in adipose tissue) [5]. Increasing circulating level of Metrnl promoted alternative activation of anti-inflammatory macrophages and increased expression of thermogenic gene in adipose tissue, subsequently stimulating energy expenditure and improving glucose tolerance in mice [5]. Since Metrnl linked the regulation of energy homeostasis and tissue inflammation, it might have therapeutic potential for metabolic inflammatory diseases, including T2DM.

Until now, several studies had investigated the circulating Metrnl level in T2DM. However, these studies had conflicting results. Four studies [6–9] reported a lower circulating Metrnl level in patients with newly diagnosed T2DM, while 2 studies [10,11], including our previous study [11], revealed a higher circulating Metrnl concentration in T2DM. In addition, scant research has explored the associations of circulating Metrnl level with β-cell function and IR in T2DM, especially in patients diagnosed type 2 diabetes. Furthermore, irisin, a secreted adipomyokine, which was also found to be induced by exercise and stimulated adipose tissue thermogenesis, was identified in 2012 by the same research team that identified Metrnl [5,12]. Although both irisin and Metrnl were found to be induced by exercise and had the capacity to stimulate adipose tissue thermogenesis, whether there was a relationship between them remains unclear.

Our study intended to explore the associations of serum Metrnl level with β-cell function and IR and further explore the correlation between Metrnl and irisin in patients with type 2 diabetes.

# Material and Methods

## Sample size calculation of T2DM participants

As we mainly explored the associations of Metrnl with other indexes in T2DM participants using multiple linear regression analysis, we could estimate the sample size of T2DM participants and the pwr package of R software was performed to calculate sample size under linear regression [13]. Furthermore, we estimated power and sample size for this test using the pwr.f2.test function. The F test has numerator and denominator degrees of freedom. The numerator degrees of freedom, u, is the number of coefficients you will have in your model (minus the intercept). In our example, $u=7$, $F2=0.3/(1–0.3)$, sig.level=0.05, power=0.8. The denominator degrees of freedom, v, is the number of error degrees of freedom: $v=n-u-1$. This implies sample size $n=v+u+1$ and the minimum size sample of T2DM participants in our study was 41.

## Participants

Our study included 59 participants with diagnosed type 2 diabetes with durations ≥ 1 year and 30 sex-, age-, and body mass index (BMI) matched healthy participants from Qilu Hospital of Shandong University from March 2019 to August 2019. The 2006 World Health Organization (WHO) criteria were used to diagnose diabetes [14]. The following participants were excluded: patients with 1) other types of diabetes; 2) severely cardiovascular diseases; 3) severely cerebrovascular diseases; 4) severely liver diseases; and 5) severely kidney diseases. The ethics committee of the Qilu Hospital of Shandong University have approved this study (Approval No. KYLL-2019-270) and all participants have provided written informed consent.

## Clinical data collection

Medication histories and comorbidities were collected by electronic medical record. BMI, waist circumference (WC), and blood pressure (BP) were measured as described previously [6, 11]. After at least a 10-hour fast, blood samples were collected for the detection of fasting blood glucose (FBG), uric acid (UA), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and hemoglobin A1c (HbA1c) levels. Body fat percentage (%) and visceral adipose tissue (VAT) area ($cm^2$) were accessed by dual-energy x-ray absorptiometry (DEXA). Circulating Metrnl level was determined by ELISA kits (Cusabio Biotech Co., Ltd., China; Catalogue No. CSB-EL013718HU). Circulating irisin level was measured using ELISA kits Adipogen Corporation, San Diego, CA, USA; Catalogue No. (AG-45A-0046YEK-KI01).

## β-cell function and IR assessment

All participants finished a 75-g oral glucose tolerance test (OGTT). At 0 and 120 minutes, blood was collected, and glucose and C-peptide were measured. Fasting glucose and C-peptide were used to calculate HOMA2 model (*www.OCDEM.ox.ac.uk*) [15]. The basal β-cell function was estimated by HOMA2-%B; the general β-cell function was presented by $AUC_{0-2}$ of C-peptide release test; the IR and insulin sensitivity were estimated by HOMA2-IR and HOMA2-%S, respectively.
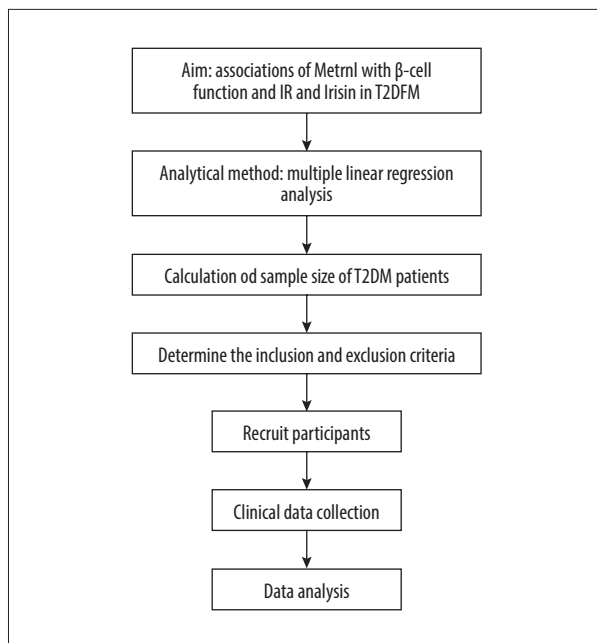
**Figure 1.** The flow chart of the study.

## Statistical analysis

The variables are presented as the mean±standard deviation (SD) or the median (interquartile range). Student's *t*-test and Mann-Whitney U test were used to detect the differences between groups for variables in normal distribution and variables in skewness distribution, respectively. The relationships between variables were analyzed by multiple linear regression analysis or Spearman correlation analysis. Statistically significant difference was defined by *P*<0.05. All statistical analyses were conducted with SPSS 22.0 software. The flow chart of the study is shown in Figure 1.

## Results

### Characteristics of study participants

The T2DM patients had higher systolic BP, FBG, postprandial blood glucose (PBG), HbA1c, TG, and lower HDL-C levels compared with the NGT group (Table 1). Compared with the NGT participants, serum Metrnl level was significantly elevated in the T2DM group (210.30 pg/mL; range 105.94–323.91 pg/mL versus 132.02 pg/mL; range 104.93–195.92 pg/mL).

### Associations of Metrnl with glucose-related indicators in T2DM group

Table 2 shows the associations of Metrnl level with glucose-related indicators in the T2DM group. We observed that Metrnl positively associated with FBG and PBG even after multiple

adjustment. Metrnl did not associate with β-cell function-related indicators (fasting C-peptide, $AUC_{0-2}$, and HOMA2-%B). On the contrary, it positively correlated with HOMA2-IR and negatively correlated with HOMA2-%S even after multiple adjustment in the T2DM group.

### Associations of Metrnl level with obesity-related indicators in the T2DM group

We then analyzed the associations of Metrnl level with obesity-related indicators in the T2DM group (Table 3). Unfortunately, we did not observe any relationship between Metrnl level and obesity-related indicators (BMI, WC, body fat percentage and VAT area).

### Associations of Metrnl with irisin level in the T2DM group

We finally analyzed the associations of Metrnl with irisin level in the T2DM group (Figure 2). Unfortunately, we did not observe the significant relationship between these 2 hormones (*r*=−0.159, *P*=0.229).

## Discussion

Metrnl, also known as subfatin, is a newly discovered adipomyokine that is mainly secreted by white adipose tissue and skeletal muscle [5,16,17]. In mice, it can increase the IL-4 expression in an eosinophil-dependent way, promote the alternative activation of anti-inflammatory macrophages and increase the expression of thermogenic gene in white adipose tissue [5]. Since Metrnl can induce macrophage activation and promote brown/beige fat thermogenesis, it might have therapeutic potential in metabolic inflammatory diseases, such as T2DM.

Since its discovery, several studies explored the relationship between circulating Metrnl level and T2DM. However, these studies did not reach a consensus. Lee et al., Zheng et al., Dadmanesh et al., and El-Ashmawy et al. [6–9] all found a lower circulating Metrnl level in newly diagnosed T2DM patients. Additionally, Lee et al. [6] and El-Ashmawy et al. [9] reported a negatively correlation between Metrnl level and HOMA-IR in study participants which included NGT, prediabetes and newly diagnosed T2DM. Dadmanesh et al. [8] also revealed a negatively correlation between Metrnl level and HOMA-IR in T2DM patients. In mice, adipocyte Metrnl could inhibit adipose inflammation and promote the differentiation, expandability, and lipid metabolism of white adipocyte through PPARγ pathway, which contributed to its activity against IR [18]. Metrnl also attenuated lipid-induced inflammation and IR via AMPK or PPARδ-dependent pathways in skeletal muscle of mice [19]. Therefore, the lack of Metrnl (lower Metrnl level in T2DM) might do not have enough capacity to antagonize IR, leading to the occurrence of T2DM.

**Table 1.** The characteristics of study participants.

| Characteristics | NGT (n=30) | T2DM (n=59) | P |
|---|---|---|---|
| Female (n,%) | 12  (40.0%) | 25  (42.4%) | 0.830 |
| Age (years) | 56.03±4.06 | 55.93±9.63 | 0.945 |
| Body mass index (kg/m²) | 25.98±2.24 | 25.92±3.31 | 0.925 |
| Waist circumference (cm) | 92.03±8.25 | 92.14±10.20 | 0.962 |
| Systolic blood pressure (mmHg) | 129.27±13.20 | 141.76±23.01 | **0.002** |
| Diastolic blood pressure (mmHg) | 78.63±7.11 | 82.58±15.66 | 0.106 |
| Fasting blood glucose (mmol/L) | 5.30±0.30 | 8.25±2.41 | **<0.001** |
| Postprandial blood glucose (mmol/L) | 5.72±0.82 | 17.22±3.92 | **<0.001** |
| HbA1c (%) | 4.91±0.35 | 8.61±1.80 | **<0.001** |
| Fasting C-peptide (ng/mL) | – | 1.44  (0.99–2.01) | – |
| 2h C-peptide (ng/mL) | – | 3.94  (2.68–5.04) | – |
| Duration of diabetes (years) | – | 10.00  (6.00–17.00) | – |
| Insulin secretagogues treatment (n,%) | – | 43  (72.9%) | – |
| Insulin treatment (n,%) | – | 26  (44.1%) | – |
| Antidiabetic treatment (n,%) | – | 54  (91.5%) | – |
| **Hypertension (n,%)** | **8  (26.7%)** | **32  (54.2%)** | **0.013** |
| **Dyslipidemia (n,%)** | **6  (20.0%)** | **30  (50.8%)** | **0.005** |
| **Diabetic kidney disease (n,%)** | **–** | **30  (50.8%)** | **–** |
| **Diabetic retinopathy (n,%)** | **–** | **16  (27.1%)** | **–** |
| Triglyceride (mmol/L) | 0.94      (0.71–1.09) | 1.66  (1.03–2.49) | **<0.001** |
| High-density lipoprotein cholesterol (mmol/L) | 1.41±0.26 | 1.12±0.35 | **<0.001** |
| Uric Acid (umol/L) | 268.83±76.08 | 293.00±81.01 | 0.171 |
| Body fat percentage (%) (n=37) | – | 31.76±6.12 | – |
| Visceral adipose tissue area (cm2) (n=37) | – | 146.52±41.51 | – |
| Metrnl (pg/mL) | 132.02  (104.93–195.92) | 210.30  (105.94–323.91) | **0.010** |
| Irisin (ng/mL) | – | 174.11  (107.94–298.18) | – |

NGT – normal glucose tolerance; T2DM – type 2 diabetes mellitus.

Oppositely, Chung et al. [10] reported a higher circulating Metrnl concentration in patients with T2DM, which was also observed in our previous study (in newly diagnosed T2DM) [11] and in this study (in previously diagnosed T2DM patients). Moreover, we found a positively correlation of Metrnl level with IR, which might be explained by the finding of Löffler et al. [20]. They found that overexpression of Metrnl inhibited human adipocyte differentiation with lower expression of PPARγ, contributing to adipose tissue inflammation and hyperinsulinemia in human samples [20]. Additionally, the higher level of Metrnl in T2DM may be a defensive mechanism to fight metabolic stress, such as insulin or leptin resistance [10]. The contrary

results observed in these studies suggested that the effect of Metrnl on IR in T2DM needed further exploration.

Since Metrnl participated in the control of inflammatory responses [5,21] and inflammation participated in the development of β-cell dysfunction [22], it was necessary to clarify the association of Metrnl with β-cell function. As far as we known, no study has shown this relationship in T2DM in detail. Dadmanesh et al. [8] did not observe an association between Metrnl level and fasting insulin in T2DM patients. Although Lee at al. [6] did not observe an association of Metrnl level with fasting C-peptide or post-load 2-hour C-peptide; they did find

**Table 2.** Multiple linear regression analysis of the relationships between Metrnl level and glucose-related indicators in participants with type 2 diabetes.

| Independent variable | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | β Coefficient (95% CI) | *P* | β Coefficient (95% CI) | *P* | β Coefficient (95% CI) | *P* |
| FBG | 34.582 (13.918 to 55.246) | **0.001** | 33.387 (12.095 to 54.679) | **0.003** | 37.551 (15.421 to 59.681) | **0.001** |
| PBG | 22.820 (10.295 to 35.345) | **0.001** | 20.857 (6.666 to 35.048) | **0.005** | 24.108 (8.763 to 39.454) | **0.003** |
| HbA1c | 2.599 (−27.696 to 32.894) | 0.864 | −0.678 (−32.056 to 30.699) | 0.966 | −6.342 (−40.088 to 27.404) | 0.707 |
| Fasting C-peptide | 38.014 (−34.685 to 110.714) | 0.299 | 55.721 (−20.873 to 132.316) | 0.150 | 68.803 (−16.459 to 154.066) | 0.111 |
| AUC0-2 | 10.443 (−14.204 to 35.090) | 0.400 | 14.245 (−10.559 to 39.049) | 0.255 | 12.693 (−14.314 to 39.700) | 0.350 |
| HOMA2-%B | −0.726 (−1.585 to 0.133) | 0.096 | −0.594 (−1.474 to 0.286) | 0.182 | −0.735 (−1.657 to 0.188) | 0.116 |
| HOMA2-%S | −2.018 (−4.593 to 0.557) | 0.122 | −2.509 (−5.160 to 0.142) | 0.063 | −3.192 (−6.254 to −0.129) | **0.041** |
| HOMA2-IR | 20.917 (−5.568 to 47.403) | 0.119 | 27.513 (−0.312 to 55.337) | 0.053 | 34.659 (3.921 to 65.397) | **0.028** |

Model 1: Unadjusted. Model 2: Age, gender and BMI adjusted. Model 3: Model 2 plus SBP, TG, HDL-C and duration of diabetes adjusted. BMI – body mass index; SBP – systolic blood pressure; TG – triglycerides; HDL-C – high-density lipoprotein cholesterol; FBG – fasting blood glucose, PBG – postprandial blood glucose; HbA1c – hemoglobin A1c.

**Table 3.** Multiple linear regression analysis of the relationships between Metrnl level and obesity-related indicators in participants with type 2 diabetes.

| Characteristics | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | β Coefficient (95% CI) | *P* | β Coefficient (95% CI) | *P* | β Coefficient (95% CI) | *P* |
| BMI | −2.256 (−18.720 to 14.207) | 0.785 | 0.655 (−16.178 to 17.488) | 0.938 | −1.603 (−20.004 to 16.798) | 0.862 |
| WC | −1.038 (−6.384 to 4.309) | 0.699 | 0.288 (−5.135 to 5.712) | 0.916 | 0.004 (−5.856 to 5.863) | 0.999 |
| Body fat percentage (%) (n=37) | 5.737 (−6.976 to 18.451) | 0.366 | 2.238 (−17.521 to 21.998) | 0.819 | −1.097 (−22.883 to 20.690) | 0.919 |
| VAT area (cm²) (n=37) | 0.238 (−1.656 to 2.133) | 0.800 | 0.553 (−1.426 to 2.532) | 0.574 | 0.754 (−1.459 to 2.967) | 0.491 |

Model 1: Unadjusted. Model 2: Age and gender adjusted. Model 3: Model 2 plus SBP, TG, HDL-C and duration of diabetes adjusted. BMI – body mass index; WC – weight circumference; VAT – visceral adipose tissue; SBP – systolic blood pressure; TG – triglycerides; HDL-C – high-density lipoprotein cholesterol.

a positively correlation between Metrnl level and HOMA-β in study participants which included NGT, prediabetes and new onset T2DM. The relationship between Metrnl and β-cell function in diagnosed T2DM has been unclear. In the present study, considering the insulin usage, we measured C-peptide to reflect β-cell function. Basal β-cell function was presented by fasting C-peptide and HOMA2-%B, general β-cell function was presented by the AUC$_{0-2}$ of C-peptide. Unfortunately, the correlation between Metrnl level and β-cell function-related indicators was not shown, indicating that Metrnl might not participate in regulating β-cell function.
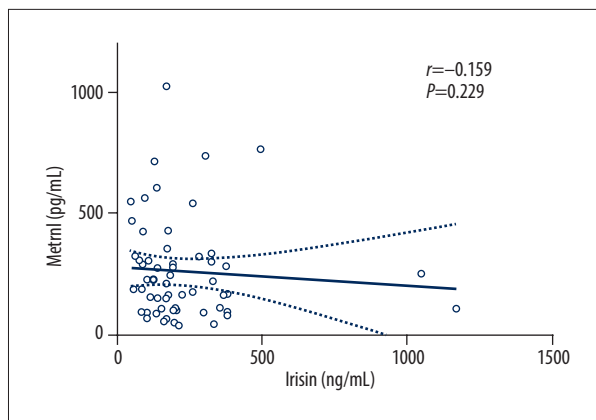
**Figure 2.** Spearman correlation between Metrnl and irisin level in type 2 diabetics.

Since Metrnl was highly expressed in white adipose tissue [5], its correlation with obesity had been clarified by some studies. The results also remained controversial. Löffler et al. reported that the expression of Metrnl in adipocytes was higher in obese children [20]. Oppositely, Pellitero et al. [23] found that patients with obesity showed lower Metrnl levels and Dadmanesh et al. [8] observed that circulating Metrnl negatively correlated with BMI in T2DM patients. Moreover, Chung et al. [10] did not find significant correlations between circulating Metrnl and obesity indicators in T2DM patients, which was also proved by our results. We also did not observe any correlations between Metrnl level and obesity-related indicators (BMI, WC, body fat percentage and VAT area). The correlation of Metrnl with obesity need further clarification.

In the current study, we also investigated the correlation between Metrnl and irisin level in T2DM. Both Metrnl and irisin were adipomyokines, which were induced by exercise and stimulated adipose tissue thermogenesis. We wondered whether there was a relationship between them. Unfortunately, we did not observe the significant relationship between these 2 hormones in T2DM patients. The lower circulating irisin level in T2DM had been proved in our previous study [24] and other numerous studies [25], therefore we did not compare the circulating irisin level between NGT and T2DM group any more

in this study. Besides, we had also investigated the associations of Irisin level with pancreatic β-cell function and IR in our previous study [24].

Some limitations of our study should also be mentioned. First, we included patients with previously diagnosed T2DM, the accuracy of results may be affected by insulin usage. However, we used C-peptide to calculate the indexes of β-cell function and IR, which should reduce the influence more or less, and the results of our study at least indicated that the circulating level of Metrnl in pathological conditions might not affect β-cell function significantly, especially in those diagnosed type 2 diabetes with such a disorder. Second, we only included Chinese participants in our study; whether the results could also be applicable to other ethnicities needs further verification. Third, some other potential factors affecting the secretion of Metrnl were not exclude, such as exercise. In addition, some comorbidities, such as hypertension, dyslipidemia, diabetic kidney disease, and diabetic retinopathy in this study population might also affect the level of Metrnl and should be considered in future study models. However, considering the collinearity problem of independent variables (SBP versus hypertension; TG and HDL-C versus dyslipidemia; duration of diabetes versus diabetic kidney disease and diabetic retinopathy) and since we included SBP, TG, HDL-C, and duration of diabetes in our final regression models, the comorbidities of hypertension, dyslipidemia, diabetic kidney disease, and diabetic retinopathy should not be included in the final regression model. Finally, the sample size of this study was relatively small; the results should be further proven by more studies with larger sample size.

## Conclusions

We observed that serum Metrnl level was significantly elevated in participants with diagnosed T2DM. Serum Metrnl level correlated with IR, but not with pancreatic β-cell function. Serum Metrnl level also did not correlated with irisin level in T2DM participants. The role of Metrnl in glucose metabolism needs further exploration.

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