

# Low Circulating Metrnl Levels are Linked to Higher Abdominal Fat in Elderly T2DM Patients: A Gender-Based Study

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**Objective:** Our study aimed to investigate the association between serum Metrnl levels and body fat distribution in type 2 diabetes mellitus (T2DM) patients.

**Methodology:** A total of 281 Chinese patients with type 2 diabetes mellitus (T2DM) (195 men and 86 postmenopausal women, aged  $61.37 \pm 6.50$  years, BMI  $24.88 \pm 3.10$  kg/m<sup>2</sup>) were included in the study. Measurements of body composition were obtained by dual-energy X-ray absorptiometry. Univariate and multivariate regression analyses were adjusted for age, sex, body mass index (BMI), and lipid levels, specifically android (waist/abdominal-dominant) and gynoid (hip/thigh-dominant) fat deposition. Gender-stratified analyses and restricted cubic spline models were employed.

**Results:** Serum Metrnl negatively correlated with A/G ratio ( $\beta = -0.01$ ; 95% CI:  $-0.02 \sim -0.00$ ) and android fat ( $\beta = -0.77$ ; 95% CI:  $-1.11 \sim -0.42$ ). After adjustments, associations with A/G and android fat persisted, but not with gynoid fat ( $P > 0.05$ ). Gender analysis showed stronger correlations in males (A/G:  $\beta = -0.02$ ; 95% CI:  $-0.04 \sim -0.01$ ; android fat:  $\beta = -0.85$ ;  $-1.28 \sim -0.43$ ), but not females.

**Conclusion:** Lower serum levels of Metrnl were significantly associated with increased abdominal adiposity in middle-aged and elderly patients with type 2 diabetes mellitus (T2DM), with a more pronounced correlation observed in males. These findings suggest that Metrnl may play a role in regulating abdominal obesity and metabolic dysfunction in this demographic.

**Keywords:** type 2 diabetes mellitus, metrnl, body fat distribution, lipid metabolism

## Introduction

Type 2 diabetes mellitus (T2DM) has emerged as a critical global public health challenge, with its high prevalence and associated mortality imposing substantial burdens on healthcare systems and economies.<sup>1</sup> T2DM represents a significant global public health crisis. Current data indicate that approximately 589 million adults aged 20 to 79 years are living with diabetes worldwide, corresponding to a prevalence rate of 11.1%, with over 90% of these cases attributed to T2DM. Notably, 252 million individuals remain undiagnosed. In 2024, diabetes directly caused 3.4 million deaths, accounting for 9.3% of global mortality. Projections suggest that by 2050, the number of cases will increase to 853 million, affecting 13% of the adult population.<sup>2</sup> Abdominal obesity, characterized by visceral fat accumulation, is a well-established risk factor for T2DM, exacerbating disease progression through multiple mechanisms, including disruption of glucose and lipid metabolism, chronic low-grade inflammation, and aggravated insulin resistance.<sup>3</sup>

In China, over 60% of adult diabetic patients are classified as overweight or obese. Data from a national cross-sectional survey conducted between 2015 and 2017, using Chinese BMI classification standards,<sup>4,5</sup> revealed that 42.4% of adults with type 2 diabetes mellitus (T2DM) were overweight (BMI 24.0–27.9 kg/m<sup>2</sup>), while 5.3% were classified as obese (BMI  $\geq 28.0$  kg/m<sup>2</sup>). Notably, although the overall obesity rates in the Chinese population are lower than those in Caucasian populations, there is a significant predisposition toward abdominal fat deposition, resulting in a higher prevalence of visceral adiposity. Among Chinese adults with T2DM, 39.7% meet the criteria for abdominal obesity,

defined as a visceral fat area (VFA) of  $\geq 100 \text{ cm}^2$ .<sup>6,7</sup> Strikingly, abdominal obesity affects 49.8% of overweight and 83.1% of obese T2DM patients, whereas it affects 11.5% of those with normal weight.<sup>8</sup> Growing evidence suggests that fat distribution, rather than total fat mass, plays a more critical role in metabolic health. Individuals with similar BMI values may present divergent cardiometabolic profiles,<sup>9</sup> as excessive visceral fat accumulation significantly increases the risk of cardiovascular disease (CVD) and T2DM.<sup>10,11</sup>

Meteorin Like Protein (Metrl), a recently identified adipokine, is secreted by skeletal muscle and adipose tissue in response to exercise and cold exposure.<sup>12</sup> It regulates glucose metabolism by enhancing glucose uptake and ameliorating insulin resistance.<sup>13</sup> Spiegelman et al first demonstrated Metrl's ability to improve glucose tolerance and increase energy expenditure.<sup>14</sup> Additionally, Metrl induces the expression of anti-inflammatory genes, suggesting a protective metabolic role. Li et al further revealed that adipose-specific Metrl knockout exacerbates insulin resistance in mice, whereas its overexpression confers protection.<sup>15</sup> Clinical studies support these findings: Lee et al and Zheng et al observed significantly reduced serum Metrl levels in newly diagnosed T2DM patients, which inversely correlated with hyperglycemia and insulin resistance. Similarly, Pellitero et al reported lower Metrl levels in obese individuals compared to normal-weight controls,<sup>16</sup> while Chung et al identified negative correlations between serum Metrl and waist circumference (WC), body weight, and BMI.<sup>17,18</sup> Notably, Du et al found that T2DM patients with visceral fat obesity (VFO) exhibit diminished serum Metrl levels, further implicating its role in abdominal fat metabolism.<sup>20–22</sup> Despite these advances, the relationship between serum Metrl and diabetic abdominal obesity remains underexplored. Therefore, this study aims to investigate whether circulating Metrl concentrations are associated with abdominal obesity in T2DM patients.<sup>23</sup>

Recent studies have highlighted the potential of novel therapeutic strategies, such as stimuli-responsive systems, biomimetic nanoparticles, and multifunctional co-delivery platforms, to overcome the challenges of treating metabolic diseases such as type 2 diabetes. These innovations, especially in nanoparticle-mediated immunomodulation and combination immunotherapy, have driven advances in the treatment of metabolic diseases and may provide new avenues for targeting adipokines like Metrl.<sup>24</sup> These methods are expected to further elucidate the role of Metrl in metabolic health and its potential as a therapeutic target.<sup>25</sup>

## Materials and Methods

### Study Subjects

A total of 281 participants (195 men and 86 postmenopausal women) aged 45 to 78 years (mean age  $61.4 \pm 6.5$  years) were evaluated. A cross-sectional study was conducted involving patients with type 2 diabetes who were admitted to The Second People's Hospital of Changzhou, the Third Affiliated Hospital of Nanjing Medical University between January 2023 and May 2024. Diabetes was defined according to the criteria established by the American Diabetes Association. Diabetes mellitus cases were confirmed by oral glucose tolerance testing. The study focused exclusively on men and postmenopausal women. Patients with type 1 diabetes, active hepatitis or liver cirrhosis, chronic renal failure, congestive heart failure, anemia, malignant tumors, parathyroid dysfunction, abnormal thyroid function, current infectious conditions, severe disabilities, severe malnutrition, or mental disorders were excluded from the study.

### Ethical Consideration

This study was conducted in accordance with the Declaration of Helsinki. The protocol for this research was reviewed and approved by the ethics committee of The Second People's Hospital of Changzhou, the Third Affiliated Hospital of Nanjing Medical University, Approval No. [2023]KY013-01, and informed consent was obtained from all participants prior to the examinations.

### Methodology

All subjects completed a questionnaire regarding their present and past illnesses, medical therapies, and other health-related behaviors. All participants underwent physical measurements using standardized methods. Height was measured to the nearest 0.1 cm using a height measuring instrument, while weight was recorded to the nearest 0.1 kg on

a calibrated digital platform scale, with participants wearing no outer clothing, hats, shoes, or carrying any items in their pockets. Body Mass Index (BMI) was calculated by dividing weight in kilograms by the square of height in meters ( $\text{kg}/\text{m}^2$ ). WHtR was determined by dividing Waist Circumference by Height.

## Laboratory Measurements

Fasting blood samples for MetrnI, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and creatinine (Cr) were collected in the morning after a 10-hour overnight fast. All blood samples were immediately separated by centrifugation at 1000g, aliquoted, and stored at  $-80^\circ\text{C}$ . Serum MetrnI concentrations were measured using enzyme-linked immunosorbent assay (ELISA) commercial kits (R&D Systems, Minneapolis, MN, USA). Serum levels of TC, TG, HDL-C, LDL-C, and Cr were measured enzymatically using a Cobas 8000 modular analyzer series (Roche Diagnostics GmbH, Mannheim, Germany).

Body composition was assessed using Dual-energy X-ray Absorptiometry (DXA) with a whole-body scanner (Hologic Discovery Wi, Bedford, MA, USA). This device was equipped with Hologic APEX software (version 4.5.3) for precise analysis of various body composition metrics. The specific measurement parameters included Waist Circumference (WC), Visceral Fat Area (VFA), Android Fat Percentage (the percentage of fat in the abdominal region), Gynoid Fat Percentage (the percentage of fat in the hip region), and the Android-to-Gynoid Fat Ratio (A/G, which compares abdominal fat percentage to hip fat percentage). During the measurement process, participants lay flat on the scanning bed and maintained a standardized posture. The whole-body scanner conducted a low-dose X-ray scan of the entire body. DXA technology employs two different energies of X-rays to penetrate body tissues. By detecting the degree of X-ray attenuation, it can accurately differentiate between adipose tissue, lean body mass (including muscle and bone), and bone mineral content. The Hologic APEX software further analyzes the scanned data to generate specific parameters regarding fat distribution across various body regions.

## Statistical Analysis

Data were analyzed using Free Statistics software (version 1.7; developed by Pavel Beránek, Czech Republic). Descriptive statistics were performed on all patient data. Normality of continuous variables was assessed using the Shapiro–Wilk test (or Kolmogorov–Smirnov test). Normally distributed data are presented as mean  $\pm$  standard deviation (SD), and differences between two groups were compared using the independent *t*-test. Non-normally distributed data are presented as median (interquartile range), and differences between two groups were compared using non-parametric tests (Mann–Whitney *U*-test). Categorical data are presented as frequencies (percentages). To explore potential associations between various variables and body fat distribution parameters, univariate linear regression analyses were first performed. Subsequently, to control for potential confounding factors, multivariate linear regression analyses were employed to examine the independent association between serum MetrnI levels and body fat-related indicators. Additionally, a restricted cubic spline (RCS) method was utilized to visually assess potential linear or non-linear relationships between serum MetrnI levels and body fat-related indicators. A *p*-value  $< 0.05$  was considered statistically significant.

## Results

### Clinical Characteristics of the Study Subjects

The general characteristics of the study groups are presented in [Table 1](#). Gender-stratified analysis revealed distinct metabolic profiles between the sexes. Male patients exhibited a larger waist circumference (WC) and higher levels of serum MetrnI and creatinine. In contrast, female patients demonstrated significantly higher levels of serum TC, HDL-C, WHtR, A/G, android percent fat, and gynoid percent fat. There were no significant differences in age, BMI, duration of T2DM, TG, and LDL-C.

### Relationships Between Clinical Parameters and Different Adiposity Indices

To further investigate the relationships between clinical parameters and various adiposity indices, we conducted univariate linear regression analyses ([Table 2](#)). The results indicated that sex, BMI, TG, HDL-C, LDL-C, CR, WC,

**Table 1** Comparison of General Clinical Characteristics in Patients with T2DM

Variables	Total (n=281)	Male (n=195)	Female (n=86)	P Value
Age (years)	61.37±6.50	61.07±6.82	62.07±5.68	0.234
Weight (kg)	66.89±10.11	69.91±9.42	60.04±8.12	0.000
Height (cm)	163.81±7.43	167.16±5.45	156.21±5.48	0.000
BMI (kg/m <sup>2</sup> )	24.88±3.10	24.99±2.98	24.62±3.36	0.359
WC (cm)	93.54±9.19	94.38±8.80	91.63±9.79	0.020
Duration of DM (years)	10(5,15)	9(5,14)	10(5,16)	0.295
TC (mmol/L)	4.32(3.67,4.96)	4.15(3.64,4.84)	4.60(3.81,5.14)	0.029
TG (mmol/L)	1.33(0.95,2.04)	1.31(0.95,1.95)	1.46(0.87,2.18)	0.579
LDL-c (mmol/L)	2.37(1.86,2.82)	2.37(1.78,2.79)	2.37(1.92,2.99)	0.254
HDL-c (mmol/L)	1.07(0.90,1.25)	1.04(0.87,1.22)	1.12(0.94,1.41)	0.012
Cr (μmol/L)	62.9(52.50,75.89)	67.1(57.2,77.4)	52.5(43.2,61.9)	0.000
Metrnl (pg/mL)	610.08±248.81	651.44±212.00	516.29±297.43	0.000
VFA (cm <sup>2</sup> )	129.39±47.87	129.23±45.55	129.76±53.00	0.932
WHtR	0.57±0.06	0.56±0.05	0.59±0.07	0.006
A/G (%)	1.22±0.19	1.23±0.19	1.18±0.17	0.031
Android percent fat (%)	34.63±7.55	32.28±6.54	39.94±7.01	0.000
Gynoid percent fat (%)	28.64±5.83	26.25±4.26	34.04±5.29	0.000

**Notes:** Data are means ± SD or median (interquartile range).

**Abbreviations:** BMI, Body Mass Index; WC, Waist Circumference; TC, Total Cholesterol; TG, Triglycerides; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; Cr, Creatinine; VFA, Visceral Fat Area; WHtR, Waist-to-Height Ratio, A/G, Android/Gynoid Ratio; Android Fat Percentage, Android percent fat; Gynoid Fat Percentage, Gynoid percent fat.

**Table 2** Relationships Between Clinical Parameters and Different Adiposity Indices

Variables	A/G		Android Percent Fat		Gynoid Percent Fat	
	β (95% CI)	P Value	β (95% CI)	P Value	β (95% CI)	P Value
Gender	-0.05 (-0.10~-0.01)	0.030	7.66 (5.96~9.37)	< 0.001	7.79 (6.62~8.96)	< 0.001
Age	0.00 (-0.01~0.00)	0.164	0.16 (0.02~0.29)	0.023	0.17 (0.07~0.28)	0.001
Duration of DM	0.00 (0.00~0.00)	0.532	0.00 (-0.13~0.13)	0.985	0.03 (-0.07~0.13)	0.577
Weight	0.01 (0.00~0.01)	< 0.001	0.18 (0.09~0.26)	< 0.001	0.01 (-0.06~0.08)	0.776
Height	0.00 (0.00~0.00)	0.475	-0.36 (-0.47~-0.25)	< 0.001	-0.33 (-0.42~-0.25)	< 0.001
BMI	0.02 (0.02~0.03)	< 0.001	1.36 (1.12~1.6)	< 0.001	0.63 (0.42~0.84)	< 0.001
TC	0.01 (0.00~0.03)	0.125	0.77 (0.00~1.53)	0.049	0.41 (-0.19~1.00)	0.178
TG	0.02 (0.01~0.04)	< 0.001	0.70 (0.23~1.17)	0.004	0.08 (-0.29~0.45)	0.671
HDL-C	-0.18 (-0.24~-0.11)	< 0.001	-4.93 (-7.65~-2.22)	< 0.001	0.05 (-2.1~2.19)	0.965
LDL-C	0.02 (0.00~0.05)	0.080	1.20 (0.11~2.28)	0.031	0.58 (-0.26~1.42)	0.172
Cr	0.00 (0.00~0.00)	0.021	0.00 (-0.03~0.04)	0.859	-0.02 (-0.04~0.01)	0.153
Metrnl	-0.01 (-0.02~0.00)	0.007	-0.77 (-1.11~-0.42)	< 0.001	-0.39 (-0.66~-0.12)	0.005
WC	0.01 (0.01~0.01)	< 0.001	0.43 (0.35~0.51)	< 0.001	0.16 (0.08~0.23)	< 0.001
WHtR	1.35 (1.01~1.70)	< 0.001	88.84 (77.48~100.20)	< 0.001	43.70 (32.95~54.45)	< 0.001

WHtR, and Metrnl were significantly associated with body fat distribution. Notably, Metrnl exhibited negative correlations with the adiposity index A/G ( $\beta = -0.01$ ; 95% CI:  $-0.02 \sim 0.00$ ), android percent fat ( $\beta = -0.77$ ; 95% CI:  $-1.11$  to  $-0.42$ ), and gynoid percent fat ( $\beta = -0.39$ ; 95% CI:  $-0.66$  to  $-0.12$ ).

## Relationship Between Different Adiposity Indices and the Serum Metrnl Levels

Multivariate linear regression analysis (Table 3) showed that serum Metrnl levels remained inversely associated with both A/G ratio ( $\beta = -0.01$ ; 95% CI:  $-0.02 \sim 0.00$ ) and android percent fat ( $\beta = -0.30$ ; 95% CI:  $-0.56 \sim -0.05$ ) even after adjusting for potential confounders related to Metrnl levels.

**Table 3** Relationship Between Different Adiposity Indices and the Serum Metrnl Levels

Variables	Unadjusted		Model 1		Model 2	
	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P
A/G	-0.01 (-0.02~0.00)	0.010	-0.01 (-0.02~0.00)	<0.001	-0.01 (-0.02~0.00)	0.032
Android Percent Fat	-0.77 (-1.11~-0.42)	<0.001	-0.38 (-0.63~-0.14)	<0.001	-0.30 (-0.56~-0.05)	0.022
Gynoid percent fat	-0.39 (-0.66~-0.12)	0.010	-0.03 (-0.23~0.17)	0.760	—	—

**Notes:** Model 1: adjusted for gender, age, BMI. Model 2: adjusted for gender, age, BMI, TG, HDL-C, LDL-C, and Cr. Serum Metrnl levels were modeled per 100 pg/mL change.

## Subgroup Analysis by Sex on the Association Between Serum Metrnl Levels and A/G Linear Relationship Between Serum Metrnl Levels and A/G

To further clarify the influence of sex on the Metrnl-body fat distribution relationship (Table 4), we conducted subgroup analyses and found no significant interaction effects between groups.

We further conducted a multivariate linear regression analysis in male patients (Table 5), which showed that serum Metrnl levels remained inversely associated with both the A/G ratio ( $\beta = -0.01$ ; 95% CI:  $-0.03 \sim 0.00$ ) and android percent fat ( $\beta = -0.46$ ; 95% CI:  $-0.81 \sim -0.10$ ) even after adjusting for potential confounders related to Metrnl levels.

To explore the potential impact of gender-specific factors on the relationship between serum Metrnl levels and body fat distribution, we conducted a subgroup analysis focused on patients with polycystic ovary syndrome (PCOS). However, no significant differences in Metrnl levels were observed between overweight and obese individuals with PCOS. This finding aligns with previous studies which have suggested that the influence of Metrnl on fat distribution may be moderated by other metabolic or hormonal factors specific to female patients, such as the altered hormonal profile in PCOS. These results emphasize the complexity of the relationship between Metrnl and abdominal adiposity and indicate that gender-specific conditions, such as PCOS, may alter the associations observed in a general T2DM population.

## Linear Relationship Between Serum Metrnl Levels and A/G

To further investigate the linear correlation between serum Metrnl levels and the A/G ratio, we conducted a restricted cubic spline (RCS) analysis. As illustrated in Figure 1, after adjusting for covariates such as age, sex, BMI, TG, HDL-C, LDL-C and CR, serum Metrnl levels exhibited a significant linear inverse relationship with adiposity indices. The

**Table 4** Subgroup Analysis by Sex

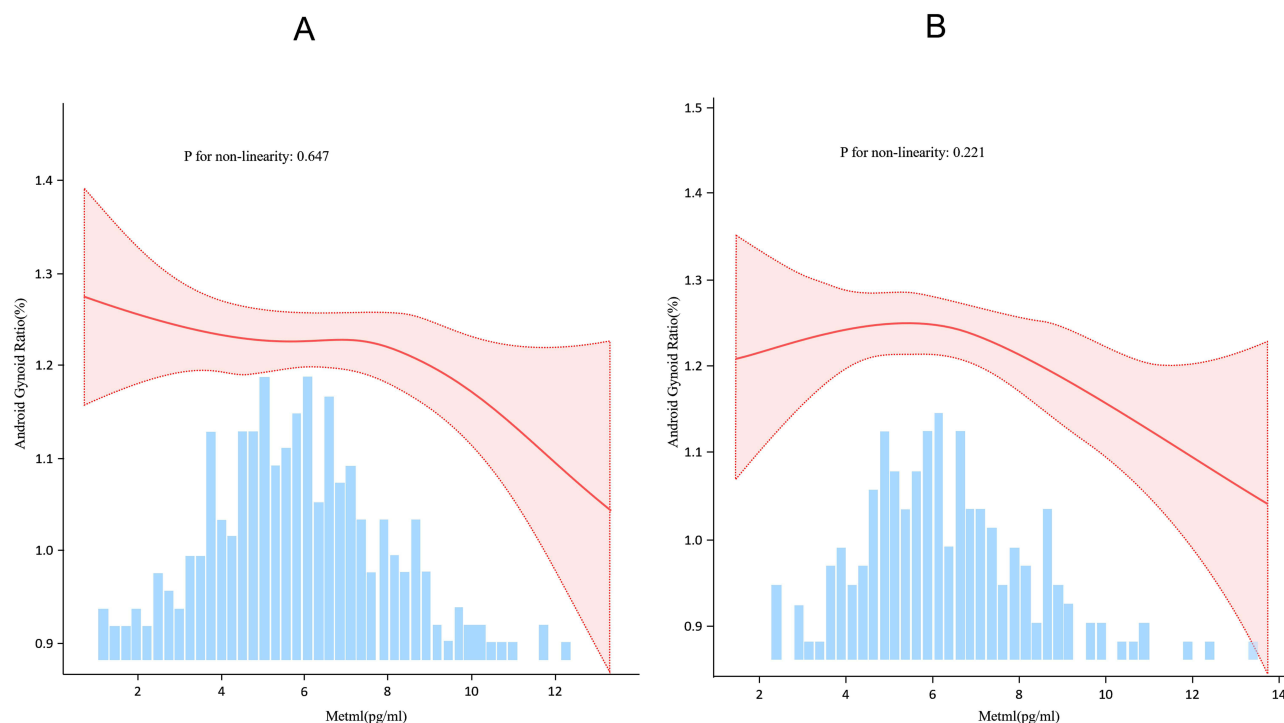
Gender	Number	Unadjusted Model	P	Adjusted Model	P	P for Interaction
Male	195	-0.02 (-0.04~-0.01)	<0.001	-0.01 (-0.03~0.00)	0.029	0.260
Female	86	0.00 (-0.02~0.01)	0.444	0.00 (-0.01~0.01)	0.968	—

**Notes:** Effect size: $\beta$  (95% CI). Adjusted model: age, BMI, TG, HDL-C, LDL-C, and Cr. Serum Metrnl levels were modeled per 100 pg/mL change.

**Table 5** Serum Metrnl and Adiposity Indices in Male Patients

Variables	Unadjusted		Model 1		Model 2	
	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P
A/G	-0.02 (-0.04~-0.01)	<0.001	-0.02 (-0.03~0.00)	0.011	-0.01 (-0.03~0.00)	0.029
Android Percent Fat	-0.85 (-1.27~-0.44)	<0.001	-0.50 (-0.83~-0.18)	0.003	-0.46 (-0.81~-0.10)	0.012

**Notes:** Model 1: adjusted for age, BMI. Model 2: adjusted for age, BMI, TG, HDL-C, LDL-C, and Cr. Serum Metrnl levels were modeled per 100 pg/mL change.



**Figure 1** Linear associations between serum MetrnI and A/G (**A**) Overall population, the p-value for non-linearity was 0.647; (**B**) Male subgroup. Adjusted for: age, BMI, TG, LDL-C, HDL-C, and CR. The p-value for non-linearity was 0.221.

restricted cubic spline analysis uses the cubic spline function to fit the nonlinear relationship between variables. The linear test result (p value) only represents the statistical significance of the linear component in the overall trend, rather than negating the potential nonlinear correlation. When  $p > 0.05$ , the linear relationship may be a reasonable simplification of the true correlation; however, even if  $p < 0.05$ , it is still recommended to combine the curve shape to explain.

## Discussion

This cross-sectional study, which included 281 participants, examined the correlation between serum MetrnI levels and body fat distribution, highlighting, for the first time, the potential influence of gender differences. The findings indicated that elevated serum MetrnI levels were significantly associated with a reduced A/G ratio (the ratio of android to gynoid fat) and a lower percentage of android fat. Conversely, lower serum MetrnI levels may suggest an increased risk of abdominal fat accumulation. Furthermore, restricted cubic spline (RCS) analysis revealed a linear relationship between serum MetrnI levels and the A/G ratio. In male T2DM patients, for every 1 unit decrease in serum MetrnI, the percentage of Android fat may increase by 0.85% (95% CI: 0.44% to 1.27%). It has been established that the A/G ratio can effectively predict insulin resistance and cardiovascular risk factors.<sup>26</sup> The A/G ratio emphasizes the relative distribution of fat rather than its absolute quantity; a higher A/G ratio indicates a greater concentration of fat in the abdominal region, which is strongly correlated with increased health risks. Previous studies have demonstrated a negative correlation between MetrnI and insulin resistance.<sup>27,28</sup> However, current literature regarding the relationship between obesity and serum MetrnI levels remains contentious. Specifically, a subgroup analysis of patients with polycystic ovary syndrome did not reveal significant differences in MetrnI levels among overweight and obese individuals.<sup>29</sup> Conversely, Wang et al observed significantly elevated serum MetrnI concentrations in obese populations, a finding supported by studies conducted on Arab populations.<sup>30</sup> These discrepancies may be attributed to ethnic differences, variations in age, gender, sample size, and the duration of diabetes. In the present study, we found that low serum MetrnI levels were closely associated with increased abdominal fat in T2DM patients, particularly among males, where the A/G ratio was independently correlated with serum MetrnI levels. To our knowledge, this is the first report demonstrating a direct link between serum MetrnI concentration and the A/G ratio. Another significant finding of this study is the independent

negative correlation between serum Metrn1 levels and the A/G ratio. Du et al confirmed that elevated serum Metrn1 levels significantly decreased with visceral fat area (VFA). While our previous research established a significant association between visceral fat obesity (VFO) and Metrn1, the current study enhances this understanding by investigating the Android-to-Gynoid Fat Ratio (a/g ratio), a metric that reflects the relative predominance of metabolically active visceral fat. This suggests that the imbalance between visceral and subcutaneous fat depots, as indicated by the a/g ratio, may serve as a more critical and independent determinant of Metrn1 dysregulation than the quantity of visceral fat alone. Additionally, the hormonal fluctuations characteristic of women, especially those related to the menstrual cycle and postmenopausal status, could modulate fat distribution and Metrn1 levels. Estrogen, for example, is known to influence fat storage patterns, favoring the accumulation of subcutaneous fat in the lower body (gynoid fat). After menopause, however, the decrease in estrogen levels leads to a shift toward more visceral fat deposition, which could potentially alter the impact of Metrn1 on fat distribution. Previous studies have shown that hormonal factors in women may mask or alter the associations between adipokines like Metrn1 and body fat distribution.<sup>19</sup> Therefore, this study goes beyond merely characterizing visceral fat accumulation, offering new insights into the significance of abdominal fat compartmental dynamics in the pathophysiology of Metrn1 and proposing the a/g ratio as a more effective tool for risk stratification. Research has indicated a statistically significant association between higher body mass index (BMI) and serum Metrn1 levels (SMD = -0.688, 95% CI: -1.348 to -0.028, P = 0.041). Pellitero et al found that patients with obesity exhibited lower serum Metrn1 levels compared to normal-weight controls. Insulin resistance is a primary contributor to T2DM. In this study involving T2DM patients, we also found no correlation between serum Metrn1 levels and body weight, BMI, or waist circumference (WC). Preclinical studies have shown that adipose tissue-specific knockout or transgenic over-expression of Metrn1 in mice did not result in changes in body weight, fat mass, or adipose tissue distribution. The results of Chung et al are consistent with ours. However, some studies have reported a significant positive correlation between Metrn1 levels and TC and BMI. Compared to normal-weight subjects, overweight and obese individuals exhibited increased serum Metrn1 levels, which were significantly positively correlated with BMI and WC. Löffler et al also reported increased Metrn1 expression in the adipose tissue of obese children compared to their lean counterparts. These inconsistencies may arise from the inherent limitations of BMI, which only reflects overall obesity and fails to accurately assess the distribution characteristics and metabolic state of adipose tissue. The predicted relationship exists independently of BMI and waist circumference, suggesting that Metrn1 may reflect fat distribution characteristics that traditional indicators cannot adequately capture.

This study performed a stratified analysis by gender, revealing stronger correlations in male patients for the A/G ratio ( $\beta = -0.01$ , 95% CI: -0.03 to 0.00) and Android Percent Fat ( $\beta = -0.85$ , 95% CI: -1.27 to -0.44), while no significant correlation was observed in Gynoid Percent Fat. In contrast, female patients exhibited no statistically significant correlations for these variables. This finding diverges from previous research, which has not extensively explored gender-specific analyses. We posit that gender differences in fat distribution may significantly contribute to this phenomenon. Typically, female patients present with a higher Gynoid Percent Fat, whereas male patients tend to exhibit a greater Android Percent Fat. The distribution pattern (eg, higher hip fat percentage) is generally associated with lower health risks. Conversely, the accumulation of abdominal fat in male patients is closely linked to metabolic risks, including insulin resistance and cardiovascular disease. However, in female patients, the correlation between Metrn1 and the A/G ratio may be obscured or diminished, potentially due to variations in fat distribution patterns and hormonal levels.

This study presents several limitations. Firstly, the cross-sectional design, while elucidating correlations between serum Metrn1 levels and parameters of body fat distribution, does not allow for the establishment of causality. Secondly, the study exclusively involved patients with T2DM and did not include a healthy control group, thereby precluding comparisons between diabetic and non-diabetic populations. Furthermore, the relatively small sample size may have masked potential gender differences in the effects of Metrn1. The limitations associated with the sample size also restricted the capacity to perform comprehensive subgroup analyses, such as stratified evaluations based on age, duration of diabetes, or treatment regimen. Notably, the limited number of female participants may further constrain the generalizability of the findings. Future research should consider employing a longitudinal design, increasing both the sample size and age range, and exploring the effects of variations in Metrn1 levels on body fat distribution and metabolic health.

## Conclusion

This observational study investigated the association between circulating Metrnl levels and body fat distribution in individuals with T2DM. Our findings indicate that lower serum Metrnl levels are significantly correlated with increased abdominal adiposity, particularly visceral fat, and a higher android-to-gynoid fat ratio (A/G ratio). Notably, these associations were more pronounced in male patients, highlighting potential sex differences in fat distribution and metabolic risk. The inverse relationship between serum Metrnl and abdominal fat accumulation, especially the A/G ratio, suggests that Metrnl may play a role in regulating abdominal obesity and related metabolic dysfunction in T2DM patients.

However, it is important to acknowledge the observational nature of this study, which limits our ability to infer causality. While these results provide compelling evidence of an association between Metrnl levels and fat distribution, further mechanistic studies are necessary to elucidate the underlying biological pathways through which Metrnl influences adiposity and metabolic health. Longitudinal studies involving larger, more diverse cohorts are warranted to explore the potential clinical applications of Metrnl as a biomarker for metabolic risk stratification and to better understand its role in the pathophysiology of T2DM and its complications.

## Acknowledgments

We would like to express our sincere gratitude to Dr. Du for their invaluable guidance in the study design and execution. We also thank Dr. Zhao and Dr. Liu for their contributions to data collection and analysis. Special thanks are extended to the participants of this study for their cooperation. This research was supported by The Second People's Hospital of Changzhou, the Third Affiliated Hospital of Nanjing Medical University.

## Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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