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Association of low serum Meteorin like (Metrnl) concentrations with worsening of glucose tolerance, impaired endothelial function and atherosclerosis

Hazem M. El-Ashmawy [a,*], *Fayrouz Othman Selim* [a], *Thoraya A.M. Hosny* [b], *Hosam N. Almassry* [c]

[a] *Department of Internal Medicine, Zagazig University, Faculty of Medicine, Egypt*
[b] *Department of Clinical Pathology, Zagazig University, Faculty of Medicine, Egypt*
[c] *Department of Radio-diagnosis, Zagazig University, Faculty of Medicine, Egypt*

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ABSTRACT

Objective: Meteorin-like (Metrnl) is a novel secreted protein that has a beneficial effect on glucose homeostasis with anti-inflammatory properties. Our goal is to determine whether low serum Metrnl levels are associated with worsening of glucose tolerance, impaired endothelial function, and atherosclerosis.

Methods: This study included 260 adults, 89 of whom had normal oral glucose tolerance (nOGT), 77 with glucose tolerance impairment (GTI) and 94 with type 2 diabetes (T2DM). Insulin resistance was assessed by evaluating the homeostasis model assessment of insulin resistance (HOMA-IR). Serum Metrnl level, proinflammatory, biochemical, endothelial and atherosclerosis parameters were measured.

Results: Serum Metrnl levels decreased significantly in patients with T2DM versus subjects with nOGT ($P < 0.001$). Metrnl levels were negatively correlated with fasting blood glucose, 2-h postload glucose (2 h-PLG), fasting insulin, HOMA-IR, HbA1c, high-sensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), Carotid intima media thickness (CIMT), brachial-ankle pulse wave velocity (baPWV), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin. High serum Metrnl level was significantly correlated with reduced risk of T2DM as revealed by multivariate logistic regression analysis after control of potential risk factors for diabetes. Furthermore, the association remains significant after further adjustment for IL-6, TNF-α, hs-CRP, CIMT, baPWV, ICAM-1, VCAM-1 and E-selectin.

Conclusions: Low Serum Metrnl may be associated with worsening of glucose tolerance, impaired endothelial function and atherosclerosis. It may also be considered a possible surrogate marker of endothelial dysfunction, and atherosclerosis and an independent risk factor of T2DM.

* Corresponding author at: Zagazig University, Faculty of Human Medicine, Department of Internal Medicine, Endocrinology Unit, Zagazig City 44519, Sharkyia Governorate, Egypt.
E-mail address: hazemashmawy@zu.edu.eg (H.M. El-Ashmawy).
URL: http://orcid.org/0000-0003-3763-5643 (H.M. El-Ashmawy).

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1. Introduction

The prevalence of glucose tolerance impairment (GTI) and type 2 diabetes (T2DM) is one of the leading causes of global mortality and morbidity [1]. In these two diseases, endothelial cells, liver, fat and muscle become less sensitive or resistant to insulin [2]. Low-grade inflammation (micro-inflammation) was observed in patients with diabetes and cardiovascular diseases [3,4]. Several studies demonstrate that proinflammatory cytokines such as tumor necrosis factor (TNF-α) and interleukin-6 (IL-6) and high sensitivity C-reactive protein (hs-CRP) [5] are increased in patients with T2DM [6,7]. Plasma concentrations of the adhesion molecules were independently and strongly correlated with these inflammatory factors, suggesting that inflammation has a major role in the pathogenesis of endothelial dysfunction in diabetes [8]. Endothelial dysfunction is the first stage in the development of atherosclerosis and may serve as a marker for cardiovascular disease [9]. Atherosclerosis is a progressive, chronic, vascular and inflammatory disease [10]. Patients with diabetes have twice the risk of atherosclerosis than non-diabetic subjects [11]. Cellular adhesion molecules (CAMs), such as E-selectin and ICAM-1 are secreted by proteolytic cleavage or shedding from cell membranes. Serum levels of CAMs have been considered as alternative markers of endothelial activation or dysfunction [12]. Previous studies have shown that soluble CAMs are positively and independently related to incident T2DM. Muris et al. showed that the risk factors adjusted E-selectin and Intercellular adhesion molecule-1 (ICAM-1) had an independent association with T2DM [13]. Soluble vascular cell adhesion molecule-1 (VCAM-1) enhances adhesion of inflammatory cells to endothelial lining of the vascular wall and promotes cell migration across the endothelial layer [14]. Intercellular adhesion molecule-1 is one of the inflammatory markers related to cardiovascular risk [15]. Carotid ultrasound is used to measure the carotid intima-media thickness (CIMT) to assess cardiovascular disease in diabetic patients [16]. Brachial-ankle pulse wave velocity (baPWV), is a well- known index of arterial stiffness and can serve as a predictor of mortality in diabetic patients [17]. Meteorin-like (Metrnl), is a newly recognized secreted protein that highly enrich the white subcutaneous adipose tissue [18]. Acute bouts of exercise and acute cold exposure can clearly induce Metrnl in white adipose tissue. Furthermore, Metrnl enhances anti-inflammatory cytokines and increase genes expression associated with thermogenesis in beige/brown adipocytes [19]. High serum Metrnl level was found to stimulates IL-4 expression through eosinophil-dependent signaling which in turn stimulates the macrophages in the adipose tissue that activates the thermogenic gene and anti-inflammatory programs in adipose tissue [19]. One study showed that adipocyte specifically deficient in Metrnl, increased insulin resistance (IR) caused by a high-fat diet while adipocyte specifically overexpressed in Metrnl, inhibited IR caused by leptin deletion or a high-fat diet [20]. Lee et al. showed a decrease in serum Metrnl level which is also inversely associated with insulin resistance and glucose level in diabetic patients [21]. Previous study has shown that Metrnl inhibits IR caused by obesity through the process of improving adipose function, including metabolism activation, and anti-inflammatory action [20]. High serum Metrnl concentration improves insulin sensitivity and prompt energy expenditure in mice [19]. Serum Metrnl levels were negatively associated with different cardiovascular risk factors including metabolic syndrome components [22]. We conducted a cross-sectional study to examine the association between low serum Metrnl concentrations and worsening of glucose tolerance, impaired endothelial function and atherosclerosis markers in adult humans.

2. Subjects and methods

We recruited 260 adults who were examined at the outpatient clinic of Zagazig University Hospital, Egypt. Inclusion criteria: BMI <35 kg/m^2; age between 20 and 75 years; no history of malignancy or recent infection; no history of taking antidiabetic medications, including glucagon-like peptide, insulin and oral hypoglycemic drugs. Exclusion criteria: Patients taking concomitant medications such as systemic steroids, cholestyramine, statins, diuretics, B-blockers or oral anticoagulants; patients with psychiatric or autoimmune diseases disorders, history of myocardial infarction, heart failure, cerebrovascular accident, acute or chronic pancreatitis, high levels of alanine or aspartate aminotransferase (two folds the upper reference range), impaired renal function (serum creatinine ≥1.5 mg/dL) and women who were breastfeeding or pregnant. The study was approved by the ethics committee (Institutional review board Zagazig University - Faculty of medicine). Signed, informed written consent was obtained from all patients prior to their participation in the study. The study was conducted in accordance with the standards of the Helsinki Declaration. All subjects underwent 75-g oral glucose tolerance test (OGTT) after 10 h of fasting. The Subjects were divided into three groups according to the criteria of the American Diabetes Association, as follows: 89 with normal oral glucose tolerance (nOGT), fasting blood glucose (FPG) < 100 mg/dL with a 2-h postload glucose (2 h-PLG) of <140 mg/dL); GTI (n = 77, FPG between 100 and 125 mg/dL and 2 h-PLG 140 and 199 mg/dL); and previously unknown T2DM (n = 94, FPG ≥ 126 mg/dL or 2 h-PLG ≥ 200 mg/dL).

2.1. *Measurement of blood biochemical parameters*

Blood samples were collected after a 12-h fast to measure lipid profiles, creatinine, insulin and plasma glucose. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were estimated on a HITACHI 7450 analyzer (HITACHI, Tokyo, Japan). HbA1c was measured by a turbidimetric inhibition immunoassay (Cobas 6000, Roche Diagnostics). Plasma glucose was assessed by hexokinase method on a Hitachi 7170 analyzer (Boehringer Mannheim, Mannheim, Germany). Fasting insulin concentration was measured by chemiluminescence enzyme immunoassay. The levels of hs-CRP were analyzed using a nephelometric method. TNF-α, and IL-6 were measured using an enzyme-linked immunosorbent

assay (ELISA). VCAM-1, ICAM-1 and E-selectin were detected using a commercial ELISA test (Beckman Coulter Inc.). The homeostasis model assessment–insulin resistance (HOMA-IR) was calculated by the following formula: (FPG (mmol/l) × plasma fasting insulin (mIU/l)/22.5). Serum Metrnl level was analyzed using an ELISA kit (R&D Systems Inc., Minneapolis, MN, USA).

2.2. Measurement of carotid IMT

The CIMT was assessed using 5–12 MHz transducer of high-resolution B-mode ultrasonography by a single trained technician who was not aware of any clinical information. The definition carotid plaque was a protruding focal structure with a thickness ≥1.3 mm into the arterial lumen [23]. Carotid IMT measurements were performed using software (Intimascope; Media Cross Co., Tokyo, Japan) at area of about 1–3 cm proximal to the carotid bifurcation at 3 levels of the medial and lateral sides of the carotid artery. The maximal value of the region was considered the maximal CIMT value. The CIMT was determined as the mean of the maximal right and left IMT values.

2.3. Measurement of baPWV

Brachial-ankle pulse wave velocity was determined using an automatic waveform analysis (Fukuda VS-1000; Tokyo, Japan) through the method provided by the manufacturer. Well-trained examiner performed the test for all subjects after 10 min of rest in a supine position. The pulse volume waveforms were recorded simultaneously through cuffs connected to a plethysmographic sensor that wrapped around the ankles and brachia. The time interval (ΔT) between the wave fronts of the ankle and brachial waveforms was measured. The length from ankle to brachium (ΔL) was calculated based on the subject's height [24]. The following formula was used for calculation of baPWV: ΔL/ΔT (cm/s), then the average of right and left baPWV was used for subsequent analyses.

2.4. Statistical methods

Statistical evaluation was conducted by SPSS version 22 (IBM Inc). The data are shown as the mean ± standard deviation or as a number with a percentage for the categorical variables. Levene test for quality of variance was used for evaluating the homogeneity and normal distribution of the variables. Skewed distributed parameters were logarithmically transformed before analysis. Parameters including fasting insulin, IL-6, TNF-α, TG, hs-CRP and HOMA-IR were calculated and evaluated for significance on a log scale. Comparisons between quantitative variables were examined using Student's *t*-test or ANOVA (One Way Analysis of Variance) followed by Bonferroni post-hoc where appropriate. Relationships between the parameters were evaluated using Spearman's rank correlation coefficient and age-adjusted partial correlation analysis. To test for independent associations of serum Metrnl and other variables, multivariate logistic regression analysis was used.

3. Results

Table 1 shows subjects' characteristics according to the glucose tolerance status. Patients with T2DM had an increase in HOMA-IR, HbA1C, blood pressure (BP), TG, waist-to- hip ratio (WHR), BMI, CIMT, baPWV, hs-CRP, E-selectin, ICAM-1, VCAM-1 and a decrease in HDL-C compared with subjects with nOGT. Serum Metrnl concentrations significantly decreased among patients with T2DM (61.17 ± 18.16 pg/mL) compared with GTI group (86.32 ± 29.69 pg/mL) ($P = 0.027$) and nOGT group (112.42 ± 31.71 pg/mL) ($P < 0.001$). In all subjects, age adjusted serum Metrnl level was significantly inversely correlated with FPG, 2 h-PLG, fasting insulin, HOMA-IR, HbA1c, hs-CRP, VCAM-1, ICAM-1, E-selectin, IL-6, TNF-α, CIMT and baPWV (Table 2). The relationship between serum Metrnl levels and T2DM was examined independently of known risk factors for diabetes using multivariate logistic regression analysis as presented in Table 3. After adjusting for sex, age, BP, WHR, BMI, alcohol consumption and smoking, the high Metrnl level had a significant association with lower risk of T2DM (T2DM vs nOGT, 0.94 (0.88–0.98); T2DM vs GTI + nOGT, 0.95 (0.90–0.98). This association remains significant even after additional control of other variables (hs-CRP, IL-6 and TNF-α). Furthermore, the association remains also significant even after the addition of further control of E-selectin, ICAM-1, VCAM-1, TNF-α, IL-6, hs-CRP, baPWV and CIMT (T2DM vs nOGT, 0.92 (0.84–0.97); T2DM vs GTI + nOGT, 0.93 (0.87–0.97).

4. Discussion

This study showed that serum Metrnl levels significantly decreased in newly diagnosed T2DM patients and had significant associations with markers of endothelial dysfunction, atherosclerosis and glucose intolerance. In our study, serum Metrnl levels were significantly and negatively correlated with insulin resistance marker (HOMA-IR). Previous study showed that, newly diagnosed T2DM patients had significantly lower serum Metrnl values which were inversely associated with the plasma glucose levels and IR which is in agreement with our results [21]. These data suggest that the lower Metrnl level may be a stimulus of subclinical inflammation and IR, which increase the risk of cardiovascular disease and diabetes. This work showed that, serum Metrnl had a negative association with FPG, 2 h-PLG, fasting insulin and HbA1c. Previous studies have shown that serum Metrnl enhances insulin sensitivity and has a negative association with metabolic variables, including fasting insulin, FPG, 2 h-PLG, HbA1c and lipid levels [21,25]. In a recent study, Metrnl demonstrated a negative correlation with FPG and HOMA-IR in patients with T2DM [26]. Accordingly, we conclude that there may be an association between serum Metrnl level and glucose regulation. Causes of low serum Metrnl levels in patients with newly diagnosed T2DM are still unclear. One study found that high serum Metrnl level enhances anti-inflammatory cytokines, beige fat thermogenesis associated genes expression, glucose tolerance and stimulates energy expenditure in mice [19]. Increased evidence suggests that innate immune system activation and chronic low-grade inflammatory process are directly involved in the pathophysiology of T2DM [27]. Li

Table 1 – Biochemical and anthropometric variables across the three glucose tolerance groups.

	nOGT	GTI	T2DM	P◇
n	89	77	94	
Age (years)	52.1 ± 1.61	57.3 ± 1.55	51.6 ± 1.71	0.034
Sex (M/F)	47/42	35/42	40/54	0.004
WHR	0.86 ± 0.02	0.87 ± 0.03	0.91 ± 0.01	<0.001#
BMI (kg/m^2)	24.1 ± 0.42	26.2 ± 0.66	27.1 ± 0.41	0.003#
BP (mmHg)				
SBP	116.6 ± 1.72	124.6 ± 1.82	126.73 ± 1.83	0.007#
DBP	76.9 ± 0.91	78.1 ± 1.16	81.1 ± 0.91	0.008#
OGTT (mg/dL)				
FPG	90.9 ± 1.08	97.6 ± 1.26	149.5 ± 7.9	<0.001#
2 h-PLG	113.9 ± 1.62	167.4 ± 1.80	304.5 ± 9.7	<0.001#
HOMA-IR*	2.06 ± 0.17	3.22 ± 0.64	4.78 ± 0.41	<0.001#
HbA1C (%)	5.5 ± 0.04	6.1 ± 0.04	8.4 ± 0.65	<0.001#
FINS (pmol/l) *	52.2 ± 4.21	77.6 ± 12.34	85.3 ± 8.94	0.014#
TG (mg/dl)*	260.4 ± 15.05	322.4 ± 23.9	440.2 ± 26.5	<0.001#
HDL-C(mg/dl)	57.6 ± 1.93	56.07 ± 2.32	45.6 ± 1.16	<0.001#
E-selectin (ng/ml)	46.2 ± 1.86	48.7 ± 2.79	62.8 ± 3.24	<0.001#
VCAM-1 (ng/ml)	525.4 ± 29.06	518.4 ± 32.54	671.3 ± 39.41	0.005#
ICAM-1 (ng/ml)	252.7 ± 9.06	272.8 ± 7.45	298.8 ± 12.41	<0.001#
hs-CRP (mg/l)*	0.69 ± 0.07	0.89 ± 0.08	1.13 ± 0.16	0.003#
Metrnl (pg/mL)*	112.42 ± 31.71	86.32 ± 29.69	61.17 ± 18.16	<0.001#
IL-6 (pg/ml)*	2.7 ± 0.47	4.7 ± 1.28	6.1 ± 1.38	0.127
TNF-α (ng/ml)*	3.18 ± 0.22	3.21 ± 0.23	3.29 ± 0.28	0.875
CIMT (mm)	0.68 ± 0.16	0.78 ± 0.12	0.87 ± 0.21	<0.001#
baPWV (m/s)	13.8 ± 2.8	15.7 ± 3.1	17.8 ± 3.4	<0.001#

Data represent mean ± standard deviation unless otherwise stated. WHR, waist hip ratio; BMI, body mass index; BP, blood pressure; SBP, systolic blood pressure, DBP, diastolic blood pressure; OGTT, oral glucose tolerance test; FBG, fasting blood glucose; 2 h-PLG, 2-h postload glucose; HOMA-IR, homeostasis model assessment insulin resistance; FINS, fasting insulin; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; CIMT, Carotid intima media thickness; baPWV, brachial-ankle pulse wave velocity.

# $P < 0.0025$, nOGT in comparison with T2DM patients.

* Data logarithmically transformed for analysis.

◇ Evaluated by one-way ANOVA.

Table 2 – Age-adjusted Spearman partial correlation coefficients between serum Metrnl level and other variables.

	Spearman partial correlation coefficient (n = 260)	
	r	P
WHR	−0.072	0.231
BMI	−0.082	0.198
OGTT (mg/dL):		
FPG	−0.189	0.001
2 h-PLG	−0.164	0.008
HbA1C (%)	−0.154	0.026
HOMA-IR*	−0.132	0.042
FINS*	−0.172	0.007
hs-CRP (mg/l)*	−0.146	0.036
IL-6 (pg/ml)*	−0.235	<0.001
TNF-α (ng/ml)*	−0.223	<0.001
ICAM-1 (ng/ml)	−0.253	<0.001
VCAM-1 (ng/ml)	−0.271	<0.001
E-selectin (ng/ml)	−0.161	0.008
Carotid IMT (mm)	−0.231	0.036
baPWV (m/s)	−0.245	0.028

WHR, waist hip ratio; BMI, body mass index; FPG, fasting plasma glucose; 2 h-PLG, 2-h postload glucose; HOMA-IR, homeostasis model assessment insulin resistance; FINS, fasting insulin; hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; CIMT, Carotid intima media thickness; baPWV, brachial-ankle pulse wave velocity. #P < 0.0025, nOGT in comparison with T2DM patients.

* Data logarithmically transformed for analysis.

Table 3 – Multivariate logistic regression analyses of serum Metrnl level variables across the three glucose tolerance groups.

	T2DM vs. nOGT	T2DM vs. GTI	T2DM vs. (GTI + nOGT)
Model A	0.94 (0.88–0.98)	0.95 (0.89–0.99)	0.95 (0.90–0.98)
Model B	0.93 (0.87–0.99)	0.94 (0.88–0.98)	0.95 (0.90–0.98)
Model C	0.92 (0.84–0.97)	0.93 (0.86–0.98)	0.93 (0.87–0.97)

Model A: controlling for blood pressure, waist-to-hip ratio, BMI, sex, age, alcohol consumption and smoking. Model B: additional controlling for hs-CRP, IL-6, and TNF-α. Model C: additional controlling for hs-CRP, IL-6, TNF-α, VCAM-1, ICAM-1, E-selectin, Carotid IMT and baPWV. Data are odds ratio (95% CI).

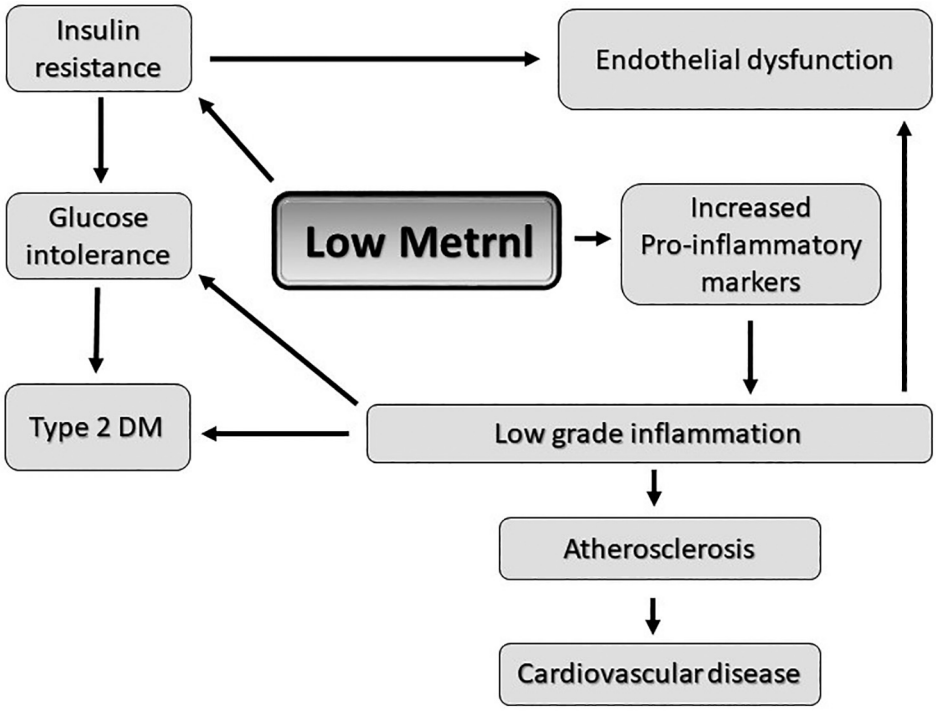

Fig. 1 – Possible mechanisms of association of low serum Metrnl level with glucose intolerance, type 2 DM, endothelial dysfunction and atherosclerosis.

et al. reported that serum Metrnl inhibits adipose tissue inflammation, promotes lipid metabolism and white adipocyte differentiation in mice [20]. In the present work, no statistically significant differences were observed in the serum Metrnl level between both sexes which is consistent with the observations of Chung et al. [22]. Also, Dadmanesh et al. reported that there was no significant difference in Metrnl level in males versus females [26]. In a recent study, serum Metrnl value showed statistically significant differences between subjects with and without chronic kidney disease [22], however subjects with renal impairment were excluded from our study. Also, we found no association between serum Metrnl concentrations and WHR and BMI, which is in agreement with findings reported by Li et al. [20]. In a recent publication, no significant differences were seen in serum Metrnl concentrations between obese and non-obese subjects. Furthermore, no association were observed between serum Metrnl value and BMI and waist circumference, in the overall group including both diabetic patients and control subjects [22]. In the present study, serum Metrnl concentrations were negatively correlated with TNF-α and IL-6. These results are in agreement with Dadmanesh et al. who found that Metrnl demonstrated a negative correlation with TNF-α and IL-6 in patients with T2DM and coronary artery disease (CAD) [26]. Also, we demonstrated that Metrnl level had a significant negative correlation with hs-CRP. Liu et al. reported that serum Metrnl level was negatively associated with hs-CRP and remained statistically significant also after control of sex, age, diabetes, alcohol intake, smoking, LDL-C, TG, TC, FBG, creatinine and BMI in CAD patients and control subjects [28]. In the present study, serum Metrnl levels were inversely associated with markers of endothelial dysfunction, namely E-selectin, VCAM-1and ICAM-1. Impairment of endothelial function is one of the main causes of various cardiovascular diseases, such as coronary heart disease, atherosclerosis and hypertension which may also be associated with insulin resistance [29]. Recent research has shown that serum Metrnl levels have negative associations with metabolic syndrome and other cardiovascular risk factors [22]. Previous study linked endothelial dysfunction with atherosclerosis, showing that, the chronic inflammatory process of atherosclerosis starts with endothelial dysfunction

[30]. Previous researches have shown that baPWV [31] and CIMT [16,32] are useful markers for assessment of atherosclerosis. Age is a major determining factor of baPWV and induces functional and structural abnormalities such as disorganization or degeneration of the medial layer and arterial wall hypertrophy [33]. In our study, age adjusted Metrnl concentrations were negatively associated with CIMT and baPWV. The mechanisms underlying the lower serum Metrnl level in endothelial dysfunction are still not understood. To date, no study has been conducted to investigate the role of Metrnl in the pathogenesis of atherosclerosis. Another study found that, there was strong induction of Metrnl in M2-like and M2 macrophages [34]. Metrnl can induce activation of M2 macrophage which leads to the stimulation of anti-inflammatory factors such as TGF-β and IL-10 and inhibition of proinflammatory cytokines such as IL-1β, IFN-γ and TNF-α [19]. Pro-inflammatory M1 macrophages have an important role in the initiation and progression of atherosclerosis, whereas the anti-inflammatory action of M2 macrophages can protect against atherosclerosis probably through plaque stabilization [35]. The possible mechanisms of association between low serum Metrnl level and glucose intolerance, T2DM, endothelial dysfunction and atherosclerosis are illustrated in Fig. 1. The results of our study suggest that serum Metrnl level may play a potential role in the pathogenesis of T2DM, endothelial dysfunction and atherosclerosis. Prospective studies are recommended to investigate the role of Metrnl in the pathogenesis of endothelial dysfunction and atherosclerosis. The conclusion of our study is that low serum Metrnl values may be associated with worsening of glucose tolerance, impaired endothelial function and atherosclerosis. Low serum Metrnl level may act as a potential risk factor of T2DM and surrogate marker for endothelial dysfunction and atherosclerosis. Therefore, modifying the serum Metrnl levels may hold promise for the development of new therapeutic agents targeting diabetes and vascular complications.

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Disclosure of potential conflicts of interest

No conflict of interest.

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