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ORIGINAL RESEARCH

Low Levels of Metrnl are Linked to the Deterioration of Diabetic Kidney Disease

Jin Chen[1,2,*], Zhi-Yong Li[2,*], Fei Xu[2,*], Chao-Qun Wang[1], Wen-Wen Li[1], Jin Lu[1], Chao-Yu Miao[2]

[1]Department of Endocrinology and Metabolism, Changhai Hospital, Second Military Medical University/Naval Medical University, Shanghai, People's Republic of China; [2]Department of Pharmacology, Second Military Medical University/Naval Medical University, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chao-Yu Miao, Department of Pharmacology, Second Military Medical University/Naval Medical University, 325 Guo He Road, Shanghai, 200433, People's Republic of China, Email cymiao@smmu.edu.cn; Jin Lu, Department of Endocrinology and Metabolism, Changhai Hospital, Second Military Medical University/Naval Medical University, 168 Chang Hai Road, Shanghai, 200433, People's Republic of China, Email lujin-sh@139.com

Objective: Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease. Metrnl is a secreted protein that plays an important role in kidney disease. The aim of this study was to investigate DKD-related factors and the correlation between serum Metrnl levels and the severity of DKD.

Methods: Ninety-six type 2 diabetes mellitus (T2DM) patients and 45 DKD patients were included in the study. A range of parameters were measured simultaneously, including waist-to-hip ratio (WHR), body mass index (BMI), urinary albumin/creatinine ratio (UACR), monocyte–lymphocyte ratio (MLR), albumin/globulin (A/G), liver and kidney function, blood lipid profile, islet function, and others. Subsequently, the related factors and predictive significance of DKD were identified. The correlation between the relevant factors of DKD and serum Metrnl levels with DKD was evaluated.

Results: The duration of the disease (OR: 1.12, 95% CI: 1.01–1.24, P=0.031), hypertension (OR: 4.86, 95% CI: 1.16–20.49, P=0.031), fasting blood glucose (OR: 1.23, 95% CI: 1.03–1.48, P=0.025), WHR (OR: 2.53, 95% CI: 1.03–6.22, P=0.044), and MLR (OR: 1.91, 95% CI: 1.18–3.08, P=0.008) are independent risk factors for DKD ($P < 0.05$). Conversely, A/G (OR: 0.13, 95% CI: 0.02–0.76, P=0.024) and Metrnl (OR: 0.99, 95% CI: 0.98–1.00, P=0.001) have been identified as protective factors against DKD. Furthermore, the level of Metrnl was negatively correlated with the severity of DKD (r_s=−0.447, P<0.001). The area under receiver operating characteristic (ROC) curves for the diagnostic accuracy of Metrnl for DKD is 0.765 (95% CI: 0.686–0.844).

Conclusion: The duration of the disease, hypertension, fasting blood glucose, WHR, and MLR are major risk factors for DKD. Metrnl and A/G are protective factors for DKD. Serum Metrnl concentrations are inversely correlated with DKD severity.

Keywords: diabetic kidney disease, urinary albumin/creatinine ratio, Metrnl, albumin/globulin

Introduction

Urinary albumin/creatinine ratio (UACR) is a recognized risk factor and a surrogate marker for microvascular disease, such as diabetic kidney disease (DKD).[1] Clinically, DKD can be divided into micro- or macro-albumin according to UACR (30–300 mg/g or >300 mg/g).[2] With the worldwide increase in diabetes prevalence, the number of DKD patients is expected to increase,[3] and it will increase by about 50% in the next 24 years, from 537 million to 783 million.[4]

DKD is a severe complication of diabetes mellitus, and it is the main cause of end-stage renal disease (ESRD) worldwide.[5,6] DKD severely reduces the quality of life of patients with long diabetic duration. Patients with DKD have higher risks of ESRD, cardiovascular disease (CVD), and even death compared to diabetic patients without kidney disease.[7] Therefore, identifying the risk and protective factors for DKD is of great importance. The pathogenesis of DKD is extremely complicated, and its underlying molecular mechanism has not yet been thoroughly elucidated. During the occurrence and development of DKD, kidney cells, including glomerular membrane cells, podocyte, endothelial cells, smooth muscle cells, and inflammatory cells are affected by hyperglycemia.[8] Many clinical biomarkers can reflect microvascular damage and are associated with the risk of microvascular disease development in T2DM patients.

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Inflammation has always been paid attention to the progress of DKD. Monocyte–lymphocyte ratio (MLR) is a novel inflammatory marker.[9] There are studies reporting a significant correlation between monocytes and serum albumin in the circulation with proteinuria.[10] Metrnl is a secreted protein expressed in various tissues of the human body, including the kidney. In 2014, Metrnl was reported as a novel adipokine with high expression in the subcutaneous white adipose tissue, and thus named as subfatin.[11] Metrnl is involved in the formation of functional white fat. By generating adipose-specific Metrnl transgenic knockout and overexpression mice, it has been demonstrated that Metrnl plays an important role in improving insulin resistance induced by a high-fat diet or leptin deficiency, and promoting insulin sensitivity.[12] Several studies have confirmed the protective effect of Metrnl in diabetes mellitus and coronary artery disease.[13–16] However, few studies have examined the relationship between serum Metrnl and diabetic microvascular complications. Therefore, this study aimed to investigate whether serum Metrnl concentration is correlated with DKD.

Materials and Methods

Study Population

A total of 141 patients with T2DM, meeting the ADA diagnostic criteria, were admitted to the Department of Endocrinology at Shanghai Changhai Hospital. To be included in the study, participants had to meet the following diagnostic criteria for T2DM: (1) fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h; (2) 2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during Oral Glucose Tolerance Test (OGTT). The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; (3) HbA1c ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial assay; (4) In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L). In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples. Participants were divided into two groups based on their UACR results: those with Normoalbuminuria (UACR < 30 mg/g, n = 96) and those with Albuminuria (UACR ≥ 30 mg/g, n = 45). Exclusion criteria included (1) acute complications such as lactic acidosis or diabetic ketoacidosis; (2) type 1 diabetes; (3) secondary diabetes mellitus; (4) severe heart, lung, and liver insufficiency; (5) mental diseases; (6) severe cerebrovascular diseases; (7) neoplasms or diseases of the blood system; (8) acute infection. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Changhai Hospital Ethics Committee. Written consent was obtained from all participants in the study. All the patients were fully informed about the purpose of the study.

Detection Index and Method

Upon admission, basic clinical data were collected, including sex, age, and diabetes history. All participants fasted for at least 8 hours overnight. The following morning, height, weight, waist circumference, and hip circumference were measured to calculate the body mass index (BMI) and waist-to-hip ratio (WHR). Fasting venous blood was collected, and a steamed bread meal test was conducted after at least 10 hours of fasting at night. Blood biochemistry and lipid profile were measured using an automatic biochemical instrument (Hitachi 7020), while fasting insulin (F-ins) and C-peptide (C-P) levels were determined by chemiluminescence (Roche). The ratio of serum albumin concentration to globulin concentration is albumin/globulin. Blood routine was determined by automatic blood cell analyzer (SYSMEX XN9000). The ratio of monocyte count to lymphocyte count is monocyte–lymphocyte ratio. The homeostasis model of insulin resistance index was used to evaluate the insulin resistance (IR) status of the patients [(fasting blood glucose (mmol/L) × fasting insulin (mIU/L))/22.5]. Serum samples were analyzed for Metrnl using a commercial ELISA kit (R&D Systems, USA).

Statistical Analysis

The Kolmogorov–Smirnov test was used initially to test the normality of the distribution of the data, with normally distributed data represented by mean ± standard deviation. The Student's *t*-test and the Mann–Whitney *U*-test were used to analyze the samples with normal and non-normal data distributions, respectively. Categorical variables were analyzed using the Chi-square test. Multivariate logistic regression was used to determine the odds ratio (OR) values and 95% confidence intervals. The

Spearman correlation was used to determine the correlation between serum Metrnl levels and UACR. For samples with non-normal distribution, differences between the three groups were assessed by the Kruskal–Wallis test to detect differences in serum Metrnl concentration in the severity of DKD. Receiver operating characteristic (ROC) curves were constructed, and the area under the curve (AUC) was calculated to assess the predictive power of the independent risk factors. All statistical analyses were performed using the SPSS 20.0 statistical software package. Statistical significance was defined as P values < 0.05.

Results

Characteristics of the Study Participants

A total of 141 patients with type 2 diabetes mellitus (T2DM) were included in the study. T2DM patients were divided into two groups: T2DM (n = 96) and DKD (n = 45). As shown in Table 1, the glycosylated hemoglobin (HbA1c) of all these T2DM patients exceeded 9%. The fasting blood glucose (FBG) of patients with DKD was significantly higher than that of patients without DKD (P<0.05). Patients with a longer duration of diabetic disease and high blood pressure are more likely to develop DKD. The WHR and MLR of patients with DKD were higher than those without DKD (all

Table 1 Clinical Characteristics of T2DM and DKD Patients

Variables	Normoalbuminuria (UACR<30 mg/g)	Albuminuria (UACR≥30mg/g)	p value
N	96	45	
Male, n (%)	48/96	21/45	0.426
Hypertension, n (%)	38/96	39/45	<0.001
Age, years	57.22±14.59	59.33±10.20	0.382
BMI, kg/m^2	25.04±3.53	26.17±4.07	0.548
Duration of diabetes, years	7.46±6.46	14.25±6.31	<0.001
TBIL, μmol/L	11.96±4.27	9.95±3.54	0.007
A/G	1.61±0.27	1.41±0.29	<0.001
MLR	0.25±0.11	0.37±0.15	<0.001
WHR	0.94±0.06	1.01±0.09	<0.001
TC, mmol/L	4.75±1.18	4.89±1.00	0.493
TG, mmol/L	1.61±1.01	1.81±0.84	0.235
LDL-C, mmol/L	2.86±0.98	2.96±0.98	0.568
HDL-C, mmol/L	1.22±0.38	1.20±0.28	0.693
Lip(a), mg/L	149.80±42.87	174.87±47.86	0.339
Uric acid, μmol/L	305.74±78.27	336.62±111.74	0.060
eGFR, mL/min per 1.73m^2	109.49±35.78	107.36±43.67	0.759
Metrnl, pg/mL	430.54±141.94	311.05±89.93	<0.001
HOMA-IR	2.57 (1.18, 4.11)	3.07 (1.56, 6.15)	0.151
FBG, mmol/L	7.55±2.53	8.77±3.46	0.02
1hBG, mmol/L	13.90±3.61	14.312.52	0.495
2hBG, mmol/L	14.93±3.87	15.52±3.39	0.381
F-C-P, μg/L	2.05±1.19	2.09±1.04	0.855
1h-C-P, μg/L	3.75±2.39	3.44±1.83	0.443
2h-C-P, μg/L	5.00±3.03	4.78±2.67	0.677
F-Ins, mIU/L	11.83±5.37	11.42±5.81	0.900
1h-Ins, mIU/L	33.56±13.17	27.39±13.33	0.286
2 h-Ins, mIU/L	36.45±17.78	37.03±19.30	0.937
HbA1c, %	9.58±4.10	9.41±2.27	0.793

Abbreviations: UACR, urinary albumin/creatinine ratio; BMI, body mass index; MLR, monocyte–lymphocyte ratio; WHR, waist-to-hip ratio; TBIL, Total bilirubin; A/G, albumin/globulin; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Lip(a), lipoprotein (a); eGFR, estimated glomerular filtration rate; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; FBG, fasting blood glucose; 1hBG, blood glucose 1 hours after meal; 2hBG, blood glucose 2 hours after meal; F-Ins, fasting insulin; 1h-Ins, insulin 1 hours after meal; 2h-Ins, insulin 2 hours after meal; F-CP, fasting C-peptide; 1h-CP, C-peptide 1 hours after meal; 2h-CP, C-peptide 2 hours after meal; HbA1c, glycosylated hemoglobin.

Table 2 Regression Analysis of Risk Factors for DKD

Variables	B	OR value	95% CI of OR	p value
Duration of diabetes, years	0.110	1.117	1.005–1.241	0.040
WHR (×10)	0.927	2.527	1.027–6.218	0.044
Hypertension, mmHg	1.582	4.864	1.155–20.488	0.031
TBIL, μmol/L	−0.168	0.846	0.708–1.010	0.168
Uric acid, μmol/L	0.163	1.004	0.998–1.010	0.163
MLR (×10)	0.008	1.908	1.183–3.076	0.008
A/G	−2.081	0.125	0.020–0.760	0.024
FBG, mmol/L	0.025	1.234	1.027–1.483	0.025
Metrnl, pg/mL	−0.011	0.989	0.982–0.996	0.001

P<0.05). A/G, total bilirubin (TBIL), and serum Metrnl in patients without DKD were significantly higher than those with DKD (all *P*<0.05). There was no significant difference in other variables between the two groups (all *P*>0.05).

Multivariate Logistic Regression Analysis of DKD

Multiple factor analysis was conducted to examine the correlation between each variable and the risk of developing DKD. The analysis revealed that the course of the disease, hypertension, WHR, FBG, and MLR were independent risk factors for DKD, and these variables were significantly correlated with DKD (all *P*<0.05). Additionally, it was found that A/G and serum Metrnl were protective factors for DKD (all *P*<0.05) (Table 2 and Figure 1). Forest map demonstrated A/G and serum Metrnl are protective factors more intuitively.

ROC Curve Analysis of Metrnl for DKD Prediction

The ROC curve analysis was performed to evaluate the predictive ability of serum Metrnl for DKD (Figure 2). When the optimal critical value was set at 404.92, the sensitivity and specificity were 0.573 and 0.844, respectively. Patients were categorized into three groups according to the UACR: normoalbuminuria (UACR <30mg/g), microalbuminuria (30 ≤ UACR ≤300mg/g), and macroalbuminuria (UACR >300mg/g). The analysis showed that there was a statistically significant difference in Metrnl among the three groups (*P*<0.05) (Figure 3).

Association of Serum Metrnl with UACR

In order to further verify the correlation between serum Metrnl and UACR, Spearman correlation coefficient was used to determine the correlation between serum Metrnl levels and UACR. The results revealed that there was a linear correlation between Metrnl and UACR (r_s=−0.447), and the difference was statistically significant (*P*<0.001) (Figure 4). At the same time, no correlation was found between serum Metrnl levels and MLR (r_s=−0.119, *P*=0.160) (Figure 5).

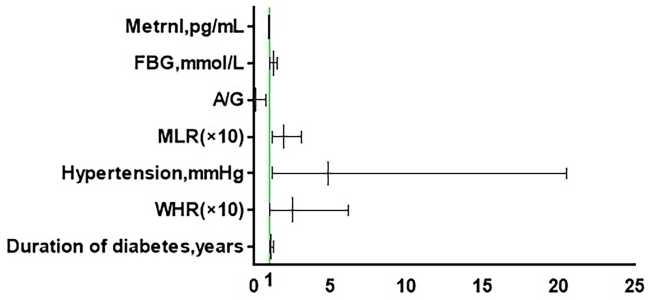

Figure 1 Forest Map for Predicting DKD. The significance of the green line represents that the OR value is equal to 1.

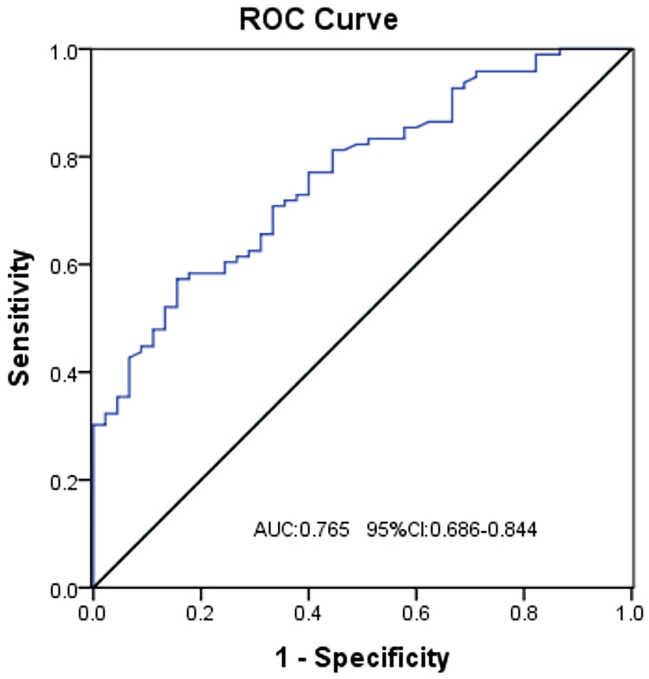

Figure 2 ROC Curve of Metrnl for Prediction of Diabetic Nephropathy.

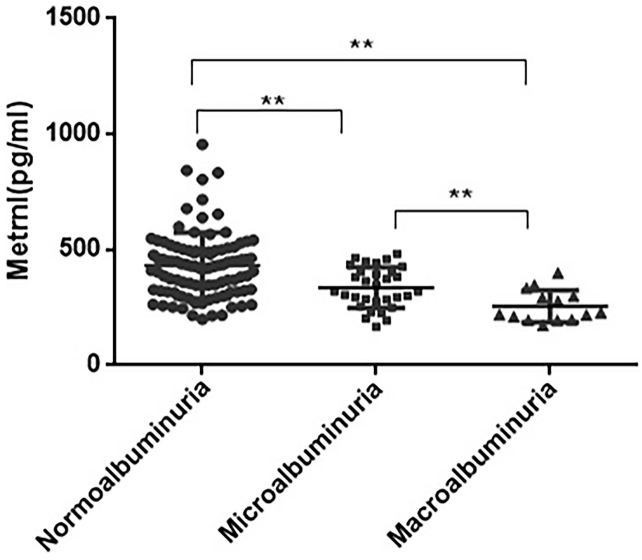

Figure 3 Serum Metrnl level decreases as with the aggravation of diabetes nephropathy. ** *P*<0.001.

Discussion

Our study analyzed 141 patients with type 2 diabetes. The main finding was that the albuminuria group had significantly lower serum Metrnl concentrations compared to the normoalbuminuria group. Logistic regression analysis demonstrated that the duration of diabetes, hypertension, WHR, MLR, and FBG were independent risk factors for DKD. Serum Metrnl level and A/G were found to be protective factors for DKD. Additionally, our study found that serum Metrnl level was associated with the severity of DKD, suggesting that Metrnl might be a promising new therapeutic target for DKD in patients.

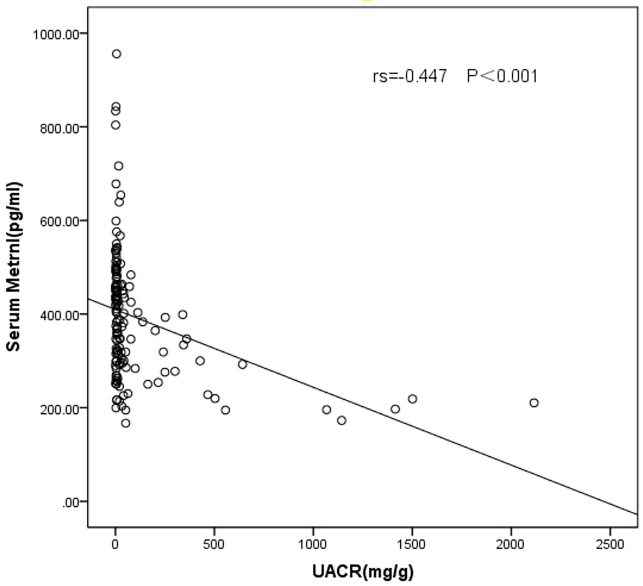

Figure 4 Association of Metrnl with the Severity of DKD.

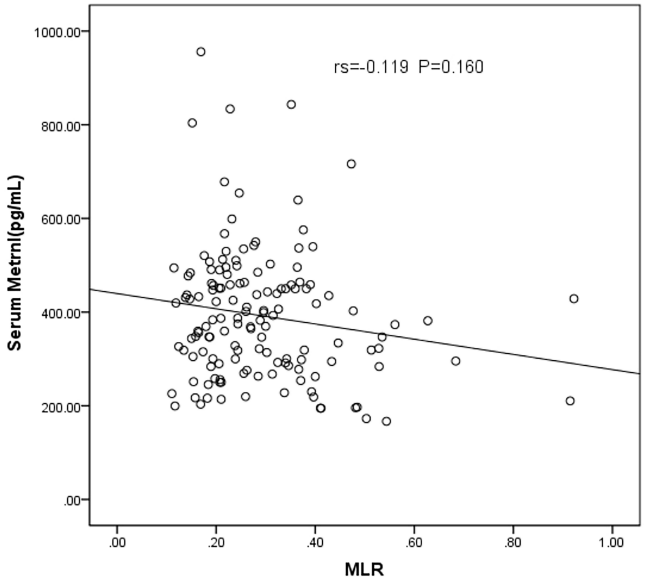

Figure 5 Association of Metrnl with MLR.

DKD, kidney damage caused by diabetes, is due to metabolic disorder, hemodynamic dysfunction, inflammation, and fibrosis. Approximately 40% of patients with T2DM and 30% of those with type 1 diabetes mellitus (T1DM) develop DKD.[3,17] In this study, we found that FBG was an independent risk factor for DKD. The proportion of DKD patients with hypertension was 86.67%, which highlights the need for clinicians to strengthen patient education and pay attention to comprehensive diabetes management.

Bilirubin, an important endogenous antioxidant,[18] is negatively correlated with urinary protein and positively correlated with eGFR in patients with T1DM[19] and T2DM[20–22] as well as in the non-diabetic population.[23,24] In 2021, the study investigating the association between serum bilirubin levels and the progression of albuminuria in Taiwanese patients with type 2 diabetes revealed that higher serum bilirubin levels were associated with a lower risk of albuminuria progression.[25] Similar results were obtained in our present study that total bilirubin in DKD patients was significantly lower than those in the

control group. Fujii et al[26] found that bilirubin protected against the progression of DKD in diabetic rats with hereditary hyperbilirubinemia by inhibiting NOX-4.

We also found that the waist-to-hip ratio (WHR) is an independent risk factor for DKD. The possible mechanism is that central or visceral adipose tissue secretes inflammatory factors, such as tumor necrosis factor-α and interleukin-6, leading to glomerular endothelial dysfunction and increased urinary albumin excretion.[27,28] The ratio of lymphocytes to monocytes (MLR) is a valuable predictor of DKD.[29] Chronic inflammatory reactions caused by abnormal metabolism are closely related to the occurrence and development of diabetes and DKD. Various immune cells and inflammatory cells such as monocytes, lymphocytes, neutrophils, and various cytokines are involved in the occurrence and development of diabetes and DKD.[30,31] Therefore, changes in leukocyte subtypes have attracted much attention in the diagnosis and treatment of DKD. In this study, the level of MLR was higher in patients with DKD compared to the control group, suggesting that DKD patients may show a more obvious inflammatory reaction. A/G is an antioxidant marker, and the level of A/G in the group with complications of diabetes decreased significantly compared to healthy subjects,[32] suggesting that the A/G ratio is a protective factor for DKD patients. Currently, there is no research on the mechanism of A/G protecting DKD, which needs to be further studied.

In recent years, there have been numerous studies on the protective effect of serum Metrnl in diabetes, coronary heart disease, and other diseases. In this study, we characterized Metrnl as a novel renoprotective factor. Adipokines participate in the regulation of multiple physiological functions, including insulin sensitivity, immunity, and inflammation.[33] Our lab has identified Metrnl as an adipokine that is abundantly expressed in rat, mouse, and human subcutaneous white adipose tissue, with relatively lower expression levels found in brown adipose tissue.[11]

We further demonstrate that transgenic mice overexpressing Metrnl specifically in adipocytes were protected from diet-induced insulin resistance. Metrnl-mediated insulin sensitization occurs through the PPARγ pathway. A number of clinical studies on diabetes have shown that serum Metrnl level in T2DM population is reduced, which is negatively correlated with HOMA-IR.[15] Previous studies have demonstrated that serum Metrnl enhances insulin sensitivity and has a negative association with metabolic variables, including fasting insulin, FBG, HbA1C, and lipid levels.[14,34] Previous research shows that Metrnl plays a role in regulating insulin resistance and inflammatory responses. Jung et al[35] determined that skeletal muscle Metrnl improved insulin sensitivity at the cellular and animal levels. Therefore, Metrnl may be used as a novel therapeutic target for the treatment of T2DM.

Recently, Metrnl was shown to be significantly associated with the pathogenesis of coronary heart disease.[13] In this study, we mainly enrolled patients with a long duration of hospitalization, and, therefore, the HOMA-IR was not calculated due to the influence of insulin use. Another study showed that the low level of serum Metrnl in patients with coronary heart disease was negatively correlated with the severity of CAD, and serum Metrnl may be a promising new therapeutic target for CAD.[36] Metrnl may play a protective role in great vessel injury through a variety of mechanisms, such as attenuating MI/R injury-induced cardiomyocyte apoptosis by alleviating endoplasmic reticulum stress via activation of AMPK-PAK2 signaling in H9C2 cells.[37] Hazem M et al's study showed that low serum Metrnl concentrations were associated with worsening of glucose tolerance, impaired endothelial function, and atherosclerosis.[15] Metrnl knockout results in impaired vasodilation function by reducing the eNOS phosphorylation level at Ser1177 and inflammatory activation by enhancing the NF-kB pathway, thus increasing the susceptibility to atherosclerosis and leading to vascular endothelial dysfunction. Exogenous Metrnl can save endothelial dysfunction induced by Metrnl deficiency. Metrnl is a therapeutic target for endothelial dysfunction and atherosclerosis.[38]

Circulating Metrnl may also be affected by disease severity. We found a negative correlation between circulating Metrnl and albuminuria. Spearman correlation analysis revealed that the serum Metrnl level of DKD patients was negatively correlated with UACR. Metrnl is a potentially important new regulator of kidney metabolism to maintain cellular mitochondrial homeostasis and lipid accumulation in DKD via Metrnl-Sirt3-AMPK/UCP1 signaling in tubular epithelial cells (RTECs).[39] The detailed mechanism accounting for serum Metrnl protecting diabetes-induced kidney injury is not entirely clear at present. A comprehensive explanation of why lower blood Metrnl is associated with and the exact function of Metrnl in diabetic kidney disease need to be explored further. The exact relationship needs to be further confirmed with more detailed, well-designed, and controlled clinical studies, especially cohort studies. Although several signaling pathways are regulated by Metrnl, Metrnl is still an orphan ligand. Reboll M et al found Metrnl as a KIT receptor ligand in the context of ischemic tissue repair.[40]

Our study should be interpreted within the context of its limitations. Firstly, the cross-sectional design of the study does not allow for causal inference. Secondly, the relatively small sample size may have underpowered the results. Thirdly, the DKD patients in our study were all inpatients, which introduces the possibility of selection bias and could confound the results. Additionally, since we only investigated Metrnl levels in Chinese patients, our findings need to be confirmed in other ethnic groups.

Conclusion

In conclusion, Metrnl was mainly expressed in renal tubules, and levels of Metrnl were significantly reduced in DKD patients. Metrnl plays a role in anti-inflammation, in consistent with previous studies reported by our lab. However, the role played by Metrnl in the kidney has not been fully explored. Although some studies have revealed the molecular mechanism of Metrnl in DKD, we need to further study its role.

Ethics Statement

Our study complies with all ethical regulations of the Changhai Hospital Ethics Committee and granted the ethical number: CHEC 2023-233.

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Disclosure

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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