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ORIGINAL RESEARCH

Serum Pigment Epithelium-Derived Factor Levels are Associated with Estradiol and Decrease After Adjusting for Alanine Aminotransferase in Chinese Women Based on Multiple Linear Regression Analysis

Cuiliu Li, Yunna Zhang, Fang Gao

The Second Department of Endocrinology, Cangzhou Central Hospital, Cangzhou, 061001, People's Republic of China

Correspondence: Cuiliu Li, Tel +8603172075935, Email licuiliu1989@163.com

Purpose: To assess changes in pigment epithelium-derived factor (PEDF) levels in patients with metabolic syndrome (MetS) and to investigate sexual dimorphism in serum PEDF levels and their relationships with estradiol.

Methods: A total of 318 individuals (145 men, 173 women) who underwent health examinations in our department were selected. Serum PEDF, estradiol and other metabolic parameters were determined. Homeostasis model assessment of insulin resistance (HOMA- IR) and homeostasis model assessment of β-cell function (HOMA-β) were calculated to evaluate insulin resistance and β-cell function, respectively. Multiple linear regression analysis was used to analyse the factors influencing serum PEDF.

Results: Serum PEDF levels were significantly higher in subjects with MetS in both men and women (12.09±2.75 vs 8.97±3.19 μg/mL in men and 11.31±2.79 vs 8.40±2.32 μg/mL in women, MetS vs non-MetS, P<0.001). Correlation analysis showed that serum PEDF levels were significantly correlated with body mass index (BMI), waist circumference, waist-to-hip ratio, diastolic blood pressure (DBP), fasting and 2-h postprandial glucose, fasting and 2-h postprandial insulin, HOMA-β, HOMA-IR, hemoglobin A1c (HbA1c), alanine aminotransferase (ALT), aspartate aminotransferase (AST), uric acid (UA), triacylglycerol (TG) and high-density lipoprotein cholesterol (HDL-C). Elevated ALT, HOMA-IR and TG were significant predictors of increased PEDF concentrations. In women, estradiol was inversely correlated with PEDF levels (r=−0.25, P=0.011), and the association was no longer significant after adjustment for ALT.

Conclusion: PEDF could be used as a biomarker of MetS in both men and women. This study reported for the first time that circulating PEDF displays sexual dimorphism, which could be related to estrogen. The association between estrogen and circulating PEDF levels was attenuated after adjusting for ALT.

Keywords: pigment epithelium-derived factor, metabolic syndrome, sexual dimorphism, estradiol, alanine aminotransferase

Introduction

With the rapid development of society and the economy, people's lifestyles have also undergone great changes, and an increasing number of people tend to live sedentary lifestyles and eat too much high-calorie food. As a result, the prevalence of metabolic syndrome (MetS) and its complications is rapidly growing worldwide and becoming an increasingly serious health problem. The latest research shows that the MetS global prevalence ranged from 12.5% to 31.4%.[1]

As a secreted glycoprotein that belongs to the superfamily of serine protease inhibitors, pigment epithelium-derived factor (PEDF) has a broad range of physiological functions, such as neuroprotection, anti-angiogenesis, anti-inflammatory, antitumourigenesis, antifibrosis and anti-ageing.[2–7] PEDF might improve metabolic abnormalities partly by inhibiting oxidative stress generation and/or inflammatory reactions in the adipose tissue and liver and act as a negative regulator of adipogenesis.[8,9] Studies have shown that circulating PEDF levels are significantly increased in subjects with MetS and its related complications, such as

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coronary heart disease, diabetes and nonalcoholic fatty liver disease (NAFLD).[10–12] PEDF is strongly linked to obesity-related insulin resistance,[13,14] and insulin resistance is the central link and common pathogenesis of various metabolic abnormalities in MetS. Studies from different populations have shown that the circulating PEDF levels of patients with MetS are significantly higher than those of patients with non-MetS, and researchers believe that PEDF could be used as a new biomarker and predictor of metabolic syndrome.[15–17]

In recent years, sexual dimorphism in the prevalence of MetS and its components has become apparent.[18] As a potential biomarker and therapeutic agent for MetS,[8] sex differences were also found in PEDF, with PEDF levels in men being significantly higher than those in women.[11,15,17,19,20] However, the evidence for the sex differences in PEDF has been limited and inconsistent, and there have also been studies showing no sexual dimorphism in PEDF concentrations.[10,16,21,22] Estradiol is the predominant circulating bioactive estrogen in premenopausal women,[23,24] and it can downregulate the expression of PEDF in tissues such as the ovary, breast, and endometrium.[25–28] A hypothesis has been suggested that the lower level of PEDF in women may be due to the suppressive effect of oestrogen,[17] but there was no evidence to support this hypothesis. Therefore, this study aimed to assess the changes in PEDF levels in patients with MetS and investigate sexual dimorphism in serum PEDF levels and their relationships with estradiol.

Methods

Study Subjects

A total of 318 individuals aged between 20 and 75 years old who underwent a health check-up in our department from January 2019 to December 2020 were included in this cross-sectional study. All participants were free of known diabetes, tumours, cardiovascular disease, hypertension, acute and chronic kidney disease, liver disease or other severe metabolic abnormalities and were not using medications that would interfere with the study outcomes; there was also no history of excessive alcohol intake in the previous 12 months. The study was approved by the Ethics Committee of Cangzhou Central Hospital and was conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent.

Clinical Measurements

All patients underwent anthropometric measurements of their blood pressure, weight, height, waist circumference and hip circumference as described elsewhere.[29] Body mass index (BMI) was calculated as the ratio of body weight in kilograms to height in metres squared. The waist-to-hip ratio was calculated as waist circumference divided by hip circumference.

Biochemical Measurements

All subjects underwent an oral glucose tolerance test (OGTT) with 75 g of glucose after overnight fasting. Blood samples for plasma glucose, insulin, hemoglobin A1c (HbA1c), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), triacylglycerol (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), estradiol and PEDF were drawn in the fasting state, and then blood samples were collected at 120 min for measurement of plasma glucose and insulin. Blood samples were centrifuged, and separated serum was kept frozen at –80 °C until assayed for estradiol and PEDF. Serum PEDF concentration was determined with a PEDF sandwich enzyme-linked immunosorbent assay kit (BioVendor, Brno, Czech Republic) according to the manufacturer's instructions, as described previously by Stejskal et al.[16] This test method has proven to be sensitive and stable in Asian, European and American populations with different metabolic profiles and in different age groups.[14,19–21,30–32] The serum estradiol level was measured by electrochemiluminescence (Immulite2000, Diagnostic Products Corp, USA). The plasma glucose concentration was tested by a hexokinase method (TBA-200FR, Tokyo, Japan). Insulin was determined by electrochemiluminescent immunoassay (Roche, USA). HbA1c was measured by high-performance liquid chromatography (HLC-73G8, Tosoh, Japan). ALT, AST, BUN, Cr, UA, and serum lipids were detected by an automatic biochemical instrument (Hitachi LABOSPECT 008AS, Tokyo, Japan); ALT and AST were detected by the kinetic method; BUN, Cr and UA were tested by the enzymatic method; TC was measured

by the cholesterol oxidase (CHOD-PAP) method; TG was measured by the glycerol lipase oxidase (GPO-PAP) method; and precipitation and direct methods were used to detect HDL-C and LDL-C.

MetS

The diagnostic criteria for MetS are based on the diagnostic criteria for MetS of the Chinese Medical Association Diabetes Society:[33] (1) abdominal obesity (central obesity): waist circumference ≥ 90 cm for men and ≥ 85 cm for women; (2) hyperglycemia: fasting plasma glucose ≥ 6.1 mmol/L or 2-hour postload plasma glucose ≥ 7.8 mmol/l and/or those who have been diagnosed with diabetes and treated; (3) hypertension: blood pressure ≥ 130/85 mmHg (1 mmHg = 0.133 kPa) and/or those who have been confirmed as having hypertension and treated; (4) fasting triglyceride (TG) ≥ 1.70 mmol/L; and (5) Fasting HDL-C < 1.04 mmol/l. MetS was defined as having three or more of the above metabolic risk factors. Subjects were divided into a MetS group and a non-MetS group according to the diagnostic criteria for MetS.

Calculations

Insulin resistance was measured by the homeostasis model assessment of insulin resistance (HOMA-IR) index, and the homeostasis model assessment of insulin secretion (HOMA-β) was calculated as basal insulin release as described previously:[34]

Formula: HOMA-IR = Fasting Insulin (FINS)× Fasting Plasma Glucose (FPG)/22.5; HOMA-β = (20 × FINS)/(FPG − 3.5).

Statistical Analysis

All data were analysed using SPSS software, version 25.0. Measurement data are expressed as the mean ± SD. Variables with skewed distributions were logarithmically transformed before analysis. The independent samples *t*-test was used for comparisons between two groups. Spearman correlation test was used to determine the relations between serum PEDF and clinical indicators. Multiple linear regression analysis was used to analyse the factors influencing serum PEDF. Differences were considered to be significant at $P < 0.05$.

Results

Clinical Characteristics of Subjects According to the Presence or Absence of MetS

A total of 318 subjects aged 20–75 years old were included in this study, with an average age of 49.73±14.76 years old, including 145 men and 173 women. The study population was divided into a non-MetS group and a MetS group. As expected, the BMI, waist circumference, waist-to-hip ratio, SBP, DBP, fasting glucose, 2-h glucose, fasting insulin, 2-h insulin, HOMA-IR, HbA1c, ALT, AST, UA, TG, TC, and PEDF in the MetS group were significantly higher than those in the non-MetS group (all P<0.05). HDL-C and estradiol in the MetS group were significantly lower than those in the non-MetS group (all P<0.05). Age, HOMA-β, BUN, Cr and LDL-C showed no significant differences between the two groups (Table 1).

The overall serum PEDF level was 10.43±3.14 μg/mL, of which the PEDF level in men was significantly higher than that in women (10.94±3.28 vs 10.01±2.96 μg/mL, P=0.006). The serum PEDF level was significantly higher in subjects with MetS in both men and women (12.09±2.75 vs 8.97±3.19 μg/mL in men and 11.31±2.79 vs 8.40±2.32 μg/mL in women, MetS vs non-MetS, P<0.001). The PEDF level in men with MetS was significantly higher than that in women with MetS, however, this difference was no longer evident in the non-MetS group (Table 1, Figure 1).

Correlation Analysis of Serum PEDF Levels and Metabolic Factors

Correlation analysis showed that serum PEDF levels were positively correlated with BMI, waist circumference, waist-to-hip ratio, DBP, fasting glucose, 2-h glucose, fasting insulin, 2-h insulin, HOMA-IR, HOMA-β, HbA1c, ALT, AST, UA and TG (all P<0.01) and were negatively correlated with HDL-C (P<0.05). No obvious correlations were found between PEDF levels and the remaining metabolic parameters (Table 2).

Table 1 Clinical Parameters of Subjects According to the Presence or Absence of MetS

	Total	Non-MetS	MetS	P value
n (men/women)	318(145/173)	130 (53/77)	188 (92/96)	0.17
Age (years)	49.73±14.76	49.55±14.84	49.86±14.73	0.858
BMI (kg/m^2)	25.52±3.88	23.69±3.24	26.81±3.79*	<0.001
Waist circumference(cm)	89.33±10.31	83.28±9.168	93.40±8.968*	<0.001
Waist-to-hip ratio	0.89±0.06	0.86±0.06	0.91±0.05*	<0.001
SBP (mmHg)	124.09±15.14	117.7±13.42	128.49±14.73*	<0.001
DBP (mmHg)	79.21±9.53	74.71±8.51	82.31±8.98*	<0.001
Fasting glucose (mmol/l)	5.81±1.46	5.28±0.88	6.18±1.67*	<0.001
2-h glucose (mmol/l)	10.19±4.30	8.44±3.55	11.41±4.36*	<0.001
Fasting insulin (μIU/mL)	13.22±9.70	9.60±6.04	15.72±10.90*	<0.001
2-h insulin (μIU/mL)	101.18±84.98	79.78±61.93	115.83±95.09*	<0.001
HOMA-IR (pmol/l, mmol/l)	3.41±2.61	2.23±1.39	4.22±2.93*	<0.001
HOMA-β (pmol/l, mmol/l)	150.69±156.83	147.05±143.77	153.24±165.71	0.474
HbA1c (%)	6.10±0.95	5.75±0.52	6.35±1.10*	<0.001
ALT (U/L)	33.18±30.64	25.13±21.69	41.80±36.13*	<0.001
AST (U/L)	27.81±16.17	24.42±10.81	31.57±19.94*	0.003
BUN (mmol/l)	5.16±1.36	5.03±1.23	5.30±1.49	0.178
Cr (μmol/l)	63.35±17.55	62.59±17.43	64.16±17.75	0.551
UA (μmo/l)	328.93±99.29	305.89±86.33	353.00±106.48*	0.001
TG (mmol/l)	1.93±1.40	1.34±0.74	2.60±1.65*	0.000
TC (mmol/l)	4.84±1.02	4.71±1.03	5.00±1.01*	0.042
HDL-C (mmol/l)	1.26±0.45	1.36±0.37	1.14±0.51*	0.000
LDL-C (mmol/l)	2.56±0.71	2.60±0.68	2.52±0.75	0.378
PEDF (μg/mL)	10.43±3.14	8.63±2.71	11.85±3.23*	<0.001
Men	10.94±3.28	8.97±3.19	12.09±2.75*	
Women	10.01±2.96	8.40±2.32	11.31±2.79*	
Estradiol	258.29±191.76	288.31±210.63	212.18±149.42*	0.034

Notes: Data are means ± SDs. Estradiol (data from women). *P<0.05.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of insulin secretion; HbA1c, hemoglobin A1c; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; TG, triacylglycerol; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PEDF, pigment epithelium-derived factor.

Factors Influencing Serum PEDF Levels

After adjusting for other metabolic indices (BMI, waist circumference, waist-to-hip ratio, DBP, fasting glucose, 2-h glucose, fasting insulin, 2-h insulin, HOMA-IR, HOMA-β, HbA1c, ALT, AST, UA, TG, HDL-C), multiple stepwise regression analysis showed that TG, ALT and HOMA-IR were independently correlated with serum PEDF (Table 3).

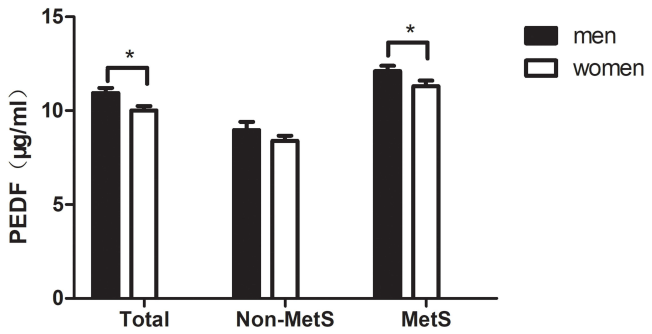

Figure 1 Analysis of circulating pigment epithelium-derived factor (PEDF) levels in different groups. Data are shown as the means ± SEs. *P<0.05.

Table 2 Spearman Correlation Analysis of PEDF and Clinical Indices

Variables	Correlation	P value
Age (years)	−0.088	0.188
BMI (kg/m^2)	0.255	<0.001
Waist circumference(cm)	0.333	<0.001
Waist-to-hip ratio	0.281	<0.001
SBP (mmHg)	0.104	0.071
DBP (mmHg)	0.203	<0.001
Fasting glucose (mmol/l)	0.188	0.001
2-h glucose (mmol/l)	0.221	<0.001
Fasting insulin (μIU/mL)	0.317	<0.001
2-h insulin (μIU/mL)	0.226	<0.001
HOMA-IR (pmol/l, mmol/l)	0.359	<0.001
HOMA-β (pmol/l, mmol/l)	0.149	0.008
HbA1c (%)	0.173	0.007
ALT (U/L)	0.374	<0.001
AST (U/L)	0.270	<0.001
BUN (mmol/l)	0.099	0.108
Cr (μmol/l)	0.105	0.161
UA (μmo/l)	0.275	<0.001
TG (mmol/l)	0.311	<0.001
TC (mmol/l)	0.105	0.127
HDL-C (mmol/l)	−0.176	0.011
LDL-C (mmol/l)	−0.02	0.771

Note: Data are means ± SDs.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of insulin secretion; HbA1c, hemoglobin A1c; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; TG, triacylglycerol; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PEDF, pigment epithelium-derived factor.

Table 3 Stepwise Multivariate Regression Analysis of Serum PEDF Levels

Independent Variable	B	SE	Standardized β	P value
ALT	0.041	0.015	0.260	0.006
HOMA-IR	0.348	0.141	0.227	0.015
TG	0.411	0.193	0.184	0.035

Note: Variables of the original model included.
Abbreviations: BMI, body mass index; Waist-to-hip ratio, waist circumference; DBP, diastolic blood pressure; 2-h glucose, Fasting glucose; 2-h insulin, Fasting insulin; HOMA- IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of insulin secretion; HbA1c, hemoglobin A1c; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UA, uric acid; TG, triacylglycerol; HDL-C, high-density lipoprotein cholesterol.

To assess whether estradiol is a potential independent contributor of serum PEDF, multiple linear regression analyses were performed among women (Table 4). In Model 1, women with higher estradiol levels had lower PEDF levels (standardized β=−0.25, P=0.011, Figure 2), and this correlation weakened but remained significant after adjusting for HOMIA-IR and TG levels (Model 2, standardized β= −0.179, P=0.037); however, after additional adjustment for ALT levels, the association between estradiol and PEDF levels was no longer obvious (Model 3, P=0.191).

Discussion

In this manuscript, we investigated the relationship between serum PEDF and MetS and explored the factors influencing circulating PEDF. Furthermore, we conducted a preliminary analysis of the causes of sex differences in PEDF. Our research revealed that serum PEDF levels were significantly increased in patients with MetS, and ALT, TG and HOMA-IR were

Table 4 Multivariate Regression Analysis of Serum PEDF Levels in Women

	B	SE	Standardized β	P
Model 1				
Estradiol	−0.004	0.002	−0.250	0.011
Model 2				
Estradiol HOMA-IR TG	−0.001 0.432 0.446	0.000 0.093 0.168	−0.179 0.418 0.195	0.037 <0.001 0.024
Model 3				
Estradiol HOMA-IR TG ALT	−0.000 0.220 0.898 0.025	0.000 0.100 0.241 0.007	−0.112 0.255 0.313 0.271	0.191 0.015 0.001 0.008

Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; TG, triacylglycerol; ALT, alanine aminotransferase.

independent risk factors for circulating PEDF and estrogens, which could be among the reasons for sex differences in serum PEDF levels.

Previous cell culture and animal model studies have shown controversial results about the role of PEDF in insulin resistance. PEDF therapy could improve insulin resistance in adipocytes and the liver but impair insulin sensitivity in skeletal muscles.[8] Although the mechanisms underlying these distinct observations are not clear, many clinical studies have supported the use of PEDF as a biomarker of various metabolic disorders. Circulating PEDF levels in patients with MetS were significantly increased and were correlated with metabolic indicators, such as waist circumference, BMI, blood lipids, blood glucose, HOMO-IR and so on, consistent with the results of previous studies.[10,11,15–17] Several biomarkers have already been proposed for MetS,[35] and there is currently no single marker that can screen for or diagnose MetS. The test method of PEDF has proven to be sensitive and robust in different populations, as mentioned above. PEDF can be a marker of insulin resistance even in healthy young people without overt metabolic or vascular disease[14] and could be useful in the prediction of MetS and cardiovascular outcomes,[17,36] which might facilitate diagnosis of MetS earlier and proactively address MetS-related complications. However, there are still many problems, such as circulating PEDF levels, that can be affected by other conditions and pathologies. Different sexes, races, and ages

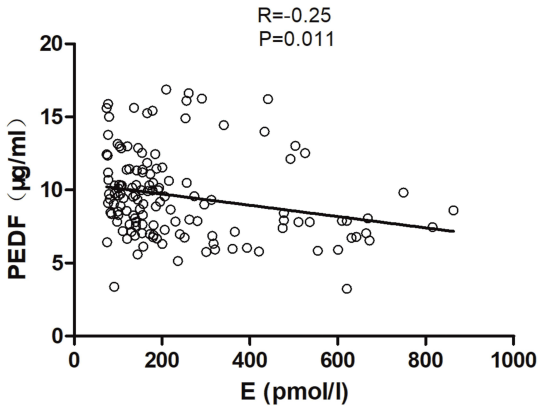

Figure 2 Correlation analysis of serum pigment epithelium-derived factor (PEDF) levels and estradiol (E) concentrations in women.

should be considering when setting the diagnostic cut-off point, and there is still a long way to go to apply it to clinical practice.

In this study, ALT, TG and HOMA-IR were independent influencing factors of circulating PEDF levels. Unlike HOMA-IR and TG, which have been shown to be unequivocally associated with PEDF,[10,11,37] a number of previous studies did not include ALT in their analysis and failed to find a correlation between PEDF and liver transaminases.[10,15,17,22] Serum aminotransferase has been regarded as a marker of nonalcoholic fatty liver disease (NAFLD) for a long time, and the accuracy of ALT in identifying NAFLD is higher than that of AST.[38] The liver is the main source of PEDF in the circulation,[39] and clinical studies have shown that serum PEDF levels are significantly elevated in patients with biopsy-proven NAFLD, and the relationship between the two is independent of other metabolic factors.[12] Some scholars believe that the reduction in PEDF levels can promote the uptake of fatty acids in the liver and the formation of lipid droplets, leading to the occurrence of NAFLD and indicating that PEDF plays an important role in the occurrence and development of hepatic steatosis.[9] In light of the above findings, PEDF could become a potential biomarker and therapeutic agent for NAFLD, but it still requires further investigation.

Similar to MetS and its components, evidence has also shown sex-based differences in serum PEDF levels, which were significantly higher in men than in women;[11,15,17,19,20] however, no sex difference was found in other studies.[10,16,21,22] In the current research, our data indicated that men have higher PEDF levels than women, and this difference was no longer evident in subjects without MetS. The above findings suggested that the sex difference in PEDF could be related to the difference in the metabolic components of the study population.

When sex is factored into disease risk, it is well established that premenopausal women are relatively protected from MetS-related diseases compared with age-matched men.[40] This "sex advantage" disappears after menopause, leading to the generally accepted conclusion that sex hormones, especially estrogens, protect against MetS. Therefore, it is not yet clear whether the reason for this sex dimorphism in PEDF is related to estrogen. In the present study, we found a significant correlation between estradiol and circulating PEDF, and this relationship persisted after adjusting for HOMA-IR and TG. However, the association was attenuated after adjusting for ALT. The prevalence and severity of NAFLD are higher in men than in women during the reproductive years; however, postmenopausal women have a higher incidence of NAFLD, and collective evidence has reflected that estrogen protects against NAFLD.[41] In the present study, the effect of estradiol on serum PEDF could be corrected by ALT, indicating that the effect of estrogen on PEDF is likely achieved mainly through amelioration of hepatic steatosis. Consistent with our results, Moreno-Navarrete et al reported that circulating PEDF and liver PEDF gene expression significantly and positively correlated with ALT, and circulating PEDF levels might be derived from the liver rather than adipose tissue, in association with metabolically induced liver damage.[39]

There are still deficiencies of this study. First, the current study did not perform liver biopsy or even liver ultrasound to clarify the liver status of the research subjects. The indices of insulin resistance were not derived directly from glucose clamp techniques, which are the gold standard for the assessment of insulin sensitivity. The strengths of our study include its relatively large sample size and broad range of metabolic profiles. This research confirmed that the PEDF level in the blood is elevated in patients with MetS and might be useful as a biomarker for its diagnosis, and importantly, we expounded on the link among PEDF, estrogen and NAFLD for the first time. This finding provides a foundation for future research to investigate the regulation of estrogen regarding circulating PEDF, which might be able to explain the metabolic changes between pre- and postmenopausal women and the metabolic differences between men and women.

Conclusions

In the present study, we confirmed that serum PEDF concentrations could be used as a biomarker of MetS and its related complications. We reported for the first time that serum PEDF displays sexual dimorphism, which could be related to estrogen, and that the association between estrogen and circulating PEDF levels was attenuated after adjusting for ALT.

Abbreviations

PEDF, pigment epithelium-derived factor; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of insulin secretion; HbA1c, hemoglobin A1c; ALT,

alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; TG, triacylglycerol; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author.

Ethical Standard Statement

The study was approved by the Ethics Committee of Cangzhou Central Hospital and and was conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent.

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Disclosure

The authors declare that they have no competing interests.

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