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ORIGINAL ARTICLE

Elevated circulating level of a cytokine, pancreatic-derived factor, is associated with metabolic syndrome components in a Chinese population

Xiaopei Cao†, Chijiao Yang†, Fenghua Lai, Zhenzhen Hong, Huimei Lin, Juan Liu, Yanbing Li*

Department of Endocrinology, First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

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***Correspondence**
Yanbing Li
Tel.: +86-020-8775-5766
Fax: +86-020-8733-2200
E-mail address: easd04lyb@126.com

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ABSTRACT

Aims/Introduction: Pancreatic-derived factor (PANDER) is an important factor involved in obesity, glucose intolerance and abnormal lipid metabolism in animals. Nevertheless, the relationship between PANDER and metabolic syndrome (MetS) in humans has not yet been reported.

Materials and Methods: To determinate the relationship between PANDER and MetS components, 212 individuals aged between 40 and 65 years were recruited. Fasting plasma PANDER and other variables were measured. Correlations of plasma PANDER and other variables were carried out. Plasma PANDER level was compared in participants with no metabolic components and those with any metabolic components, as well as in normal glucose tolerance, impaired glucose tolerance and diabetes mellitus participants.

Results: In all the participants, there were 65 participants in the no metabolic components group and 147 participants in the any metabolic components group. Plasma PANDER level was increased with the number of MetS components ($P < 0.05$) and correlated with metabolic score ($r = 0.529$, $P < 0.001$). In addition, plasma PANDER significantly correlated with fasting plasma glucose ($r = 0.187$, $P = 0.046$), 2-h plasma glucose ($r = 0.195$, $P = 0.035$), homeostasis model assessment of β-cell function ($r = -0.191$, $P = 0.039$), triglyceride ($r = 0.305$, $P = 0.001$) and high-density lipoprotein cholesterol ($r = -0.333$, $P < 0.001$). Using multivariable logistic regression analysis, circulating PANDER was associated with an increased risk ratio of impaired glucose tolerance or diabetes mellitus (odds ratio 2.22, 95% confidence interval 1.15–4.42, $P = 0.018$) after adjustment of the other possible confounders.

Conclusions: Circulating level of PANDER in relation to the accumulation in MetS suggested that persons with elevated levels of PANDER were associated with an increased risk of metabolic syndrome.

INTRODUCTION

The metabolic syndrome (MetS) is a major public health problem worldwide[1]. The clustering of hyperglycemia, hypertension, dyslipidemia (elevated serum triglyceride or low high-density lipoprotein cholesterol) and obesity, particularly central obesity, has been termed MetS[2,3]. MetS is associated with a fivefold higher risk of developing type 2 diabetes mellitus and 2.6–3-fold higher risk of cardiovascular disease in the next 5–10 years[4,5]. The pathophysiology of MetS is not well known. MetS is a consequence of complex interplay between genetic and environmental factors. It is difficult to identify a unifying molecular etiology of MetS. The components of MetS impact on each other[6]. Therefore, factors related to glucose intolerance, hypertension, dyslipidemia and obesity could lead to MetS. Several biomarkers, including leptin[7], catecholamine[8], brain natriuretic peptide[9], uric acid[10], cyctatin C[11], adipocytokine[12] and

†The first two authors contributed equally to this work and should be considered co-first authors.

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irisin[13] are thought to be associated with MetS. To date, an increasing number of studies have shown that that cytokines play an important role in the pathogenesis of MetS.

Pancreatic-derived factor (PANDER) is a cytokine that was originally described in 2002[14]. PANDER is primarily localized in both α-cell and β-cells. Increasing evidence has shown that in β-cells, PANDER and insulin co-secrete in the same secretary granules[15,16]. Initial characterization evaluating the impact of PANDER showed that it induced apoptosis of α- and β-cells of mouse and rat islets[17,18]. Recently, research has shown that chronically elevated circulating PANDER levels were observed in fatty C57Bl/6J mice[19], and there was an increased onset of high-fat diet-induced glucose intolerance in mice overexpressing PANDER compared with wild-type controls[20]. However, the effect of high-fat diet-induced glucose intolerance disappeared in PANDER knockout mice[21]. In addition, overexpression of PANDER in the livers of C57Bl/6J mice promoted lipogenesis, whereas small interfering ribonucleic acid-mediated knockdown of hepatic PANDER significantly attenuated insulin resistance and hyperglycemia in *db*/*db* mice[22]. These animal experiments suggested that PANDER might be an important factor involved in obesity, glucose intolerance and abnormal lipid metabolism, which were the major components of MetS. Nevertheless, the relationship between PANDER and metabolic components in humans has not yet been reported.

We therefore hypothesized that circulating PANDER would be associated with metabolic components in humans. It might be a possible biomarker relative to MetS. To determinate our hypothesis, we measured circulating levels of PANDER, and carried out a cross-sectional study of PANDER and metabolic variables of 212 Chinese adults.

MATERIALS AND METHODS

Participants

Individuals aged between 40 and 65 years were selected randomly from those who visited to have regular physical examinations, and matched the following criteria at the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China, during May 2012 to December 2012. The participants meeting the following inclusion criteria were included in the study: not having diabetes, not having suffered chronic liver and kidney diseases or any previous cardiovascular episode, not being pregnant, not presenting cognitive impairment that interferes with understanding of the study, and agreeing to participate in it. All participants gave informed consent before participating in this study, and the Human Research Ethics Committee of First Affiliated Hospital, Sun Yat-sen University approved the study design. The criteria of the Chinese Diabetes Society was used in the diagnosis of MetS: impaired glucose tolerance (IGT), diabetes mellitus, overweight and obesity[23]. Metabolic scores (0, 1, 2, 3, 4) were calculated using MetS components (abdominal obesity, hypertension, dyslipidemia, hyperglycemia). Participants without any MetS component were termed the non-MetC group, and those having MetS components were defined as the MetC group. Overweight was defined as body mass index (BMI) of 24–28 kg/m^2 and obesity as BMI ≥28 kg/m^2. Abdominal obesity was defined as waist circumference of ≥90 cm in men and ≥85 cm in women.

Measurement of clinical biomarkers

The 75-g oral glucose tolerance test and blood biochemical measurements were carried out for each participant. Blood samples were collected by venipuncture after an overnight fast, and other blood samples were drawn after the 75-g oral glucose tolerance test. Plasma or serum was centrifuged (1500 *g* for 15 min at 4°C) and stored at −20°C until measurement within a couple days for biochemical markers, such as fasting plasma insulin (FIns), fasting plasma glucose (FPG), 2-h plasma glucose (2hPG), glycated hemoglobin (HbA1c), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c) and serum uric acid; renal and liver function were measured enzymatically in the center laboratory of First Affiliated Hospital, Sun Yat-sen University. Homeostasis model assessment of β-cell function (HOMA-β) was calculated as FIns (IU/mL) × 20/(FPG [mmol/L]−3.5), and HOMA of insulin resistance (IR) = FIns (IU/mL) × FPG (mmol/L)/22.5 was used to evaluate insulin resistance[24].

Measurement of PANDER

Fasting plasma PANDER concentration was measured using enzyme-linked immunosorbent assay kits (Uscn Life Science Inc., Wuhan, China). The sensitivity of the assay was 0.01 ng/mL, and the linear range of the standard was 0.31–20.00 ng/mL. The intra-assay variation was 7.3%, and inter-assay variation was 6.1%.

Statistical analysis

Statistical analysis was carried out using SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA). Continuous data were summarized as either mean ± standard deviation or median and quartiles, and categorical data were expressed as percentages. Data were compared by unpaired *t*-test or Mann–Whitney *U*-tests where appropriate. We calculated Spearman's correlation coefficients to evaluate the correlations between PANDER and selected variables. To evaluate the association of PANDER with IGT, we constructed multivariable logistic regression models to assess whether circulating PANDER was associated with IGT. We calculated the odds ratio (OR) for the presence of IGT in quartiles of PANDER, with participants in the lowest quartile of PANDER considered the referent group. Adjustments were carried out for age, sex, BMI, waist circumference, FPG, 2hPG, TG and HDL-c. Two-sided *P*-value <0.05 were considered significant.

RESULTS

Clinical characteristics and metabolic components

The clinical characteristics of participants are shown in Table 1. A total of 65 participants in the non-MetC group and 147 par-

Table 1 | Participant characteristics

Characteristic	non-MetC (n = 65)	MetC (n = 147)	P-value
Age (years)	49.5 ± 8.7	51.2 ± 7.3	0.940
Female (%)	12 (42.9%)	45 (57.7%)	0.192
BMI (kg/m^2)	22.1 ± 4. 1	24.8 ± 6.8	0.108
Waist circumference (cm)	78.6 ± 8.4	80.8 ± 11.5	0.324
FPG (mmol/L)	4.51 ± 0.72	5.22 ± 0.84	<0.001
2hPG (mmol/L)	6.02 ± 2.91	7.21 ± 2.53	<0.001
FIns (IU/mL)	5.91 ± 3.73	8.65 ± 4.02	<0.001
HOMA-β	93.61 ± 57.73	86.37 ± 49.43	<0.001
HOMA-IR	1.75 ± 0.78	1.96 ± 0.94	0.097
HbA1c (%)	4.93 ± 1.71	5.01 ± 2.65	0.477
TG (mmol/L)	1.02 ± 0.32	1.65 ± 0.81	<0.001
TC (mmol/L)	5.41 ± 0.91	5.30 ± 1.04	0.510
LDL-c (mmol/L)	3.54 ± 0.92	3.64 ± 0.92	0.611
HDL-c (mmol/L)	1.62 ± 0.44	1.43 ± 0.31	<0.001
SBP (mmHg)	110 ± 8	122 ± 20	<0.001
DBP (mmHg)	68 ± 7	75 ± 10	<0.001
BUN (mmol/L)	5.3 ± 1.2	5.3 ± 1.3	0.393
Cr (μmol/L)	64.3 ± 15.7	68.4 ± 18.2	0.053
UA (μmol/L)	316.5 ± 91.0	321.6 ± 98.7	0.094
ALT (IU/L)	18.60 ± 11.33	20.07 ± 17.84	0.161
AST (IU/L)	21.35 ± 6.54	23.34 ± 9.69	0.152

n = 212. 2hPG, 2-h postprandial glucose; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; Cr, serum creatinine; DBP, diastolic blood pressure; FIns, fasting plasma insulin; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL-c, high density lipoprotein cholesterol; HOMA, homeostasis model assessment; LDL-c, low density lipoprotein cholesterol; MetC, metabolic components; SBP, systolic blood; TC, total cholesterol; TG, triglyceride; UA, serum uric acid.

ticipants in the MetC group took part in the study. The age of participants and the proportion of women were not different between these two groups (P = 0.940, P = 0.192, respectively). In our study, the 95% confidence interval (CI) of BMI of participants was 23.2–24.1 kg/m^2, and the 95% CI of waist circumference was 80.70–82.92 cm. In the MetC group, BMI and waist circumference were similar to those in the non-MetC group (P = 0.108, P = 0.324, respectively), and FPG, 2hPG, FIns were higher in participants with Mets components than those without Mets components (P < 0.001). In addition, TG was higher and HDL-c was lower in participants in the MetC group compared with those in the non-MetC group (both P < 0.001).The participants in the MetC group were more likely to suffer from raised systolic blood pressure and diastolic blood pressure when compared with the non-MetC group (both P < 0.001). However, no differences were observed in circulating levels of HbA1c, TC, LDL-c, blood urea nitrogen, creatinine, serum uric acid, alanine aminotransferase and aspartate aminotransferase between the two groups. The β-cell function measured by HOMA-β was better in the non-MetC group (P < 0.001), but HOMA-IR was not significantly different between these two groups (P = 0.097).

Association of plasma PANDER with clinical variables

Plasma PANDER powerfully correlated with FPG, 2hPG, HOMA-β, TG, HDL-c and metabolic score (Table 2). FPG and 2hPG were positively correlated with plasma PANDER (r = 0.187, P = 0.046; r = 0.195, P = 0.035, respectively), but HOMA-β had a negative correlation with plasma PANDER (r = –0.191, P = 0.039). In addition, circulating levels of PANDER positively associated with TG (r = 0.305, P = 0.001) and negatively correlated with HDL-c (r = –0.333, P < 0.001). In Figure 1, plasma PANDER levels elevated with the increasing number of MetS components (P < 0.05).

Association of plasma PANDER with the presence of IGT or diabetes mellitus

Of the participants in the normal glucose tolerance, IGT and diabetes mellitus groups, the diabetes mellitus group showed significantly elevated plasma PANDER levels compared with the normal glucose tolerance and IGT groups (both P < 0.05). Similarly, plasma PANDER levels were higher in IGT participants than normal glucose tolerance participants (P < 0.05; Figure 2). In logistic regression analyses, circulating PANDER levels in the fourth quartile were significantly associated with a higher OR of onset of IGT or diabetes mellitus (Table 3). This association remained significant after adjustment for age, sex, BMI, waist circumference, FPG, 2hPG, TG and HDL-c, with an OR of 2.22 (95% CI 1.15–4.28) for the fourth PANDER quartile (P = 0.018).

DISCUSSION

The present study, to the best of our knowledge, is the first to report that circulating PANDER is associated with the accumulation in MetS components in humans. Plasma PANDER is also a positive predictor of IGT or diabetes mellitus. The main finding of the present study is that circulating PANDER might be a possible target to prevent the further development of MetS or diabetes.

Increasing evidence has shown that PANDER co-secreted with insulin in the same secretary granules in β-cells[15,16], which implied that PANDER might act as a circulating hormone involved in regulating metabolic homeostasis. Data generated from PANDER animal models have shown that PANDER shared the pathogenesis of multiple metabolic abnormalities[25,26]. Testing the association of circulating PANDER with MetS conditions in humans, such as obesity and diabetes, might be helpful in elucidating the pathology of these conditions. In the present study, we found that elevated plasma PANDER was significantly associated with increasing the total number of MetS components, which was consistent with results from animal studies. To identify which MetS factor had a close relationship with circulating PANDER levels, we carried out correlation analyses. The results showed that FPG, 2hPG, and TG were positively correlated with plasma PANDER and HOMA-β; HDL-c had a negative correlation; whereas there were no significant associations of circulating PANDER with

Table 2 | Spearman's correlations between pancreatic-derived factor and selected variables

Characteristic	*r*	*P*-value
Age (years)	0.050	0.593
Female (%)	0.100	0.285
BMI (kg/m^2)	0.177	0.057
Waist circumference (cm)	0.129	0.113
FPG (mmol/L)	0.187	0.043
2hPG (mmol/L)	0.195	0.035
FIns (IU/mL)	0.001	0.993
HOMA-β	−0.191	0.039
HOMA-IR	0.172	0.066
HbA1c (%)	0.166	0.074
TG (mmol/L)	0.305	0.001
TC (mmol/L)	−0.075	0.426
LDL-c (mmol/L)	−0.108	0.238
HDL-c (mmol/L)	−0.333	<0.001
SBP (mmHg)	0.081	0.401
DBP (mmHg)	0.102	0.280
BUN (mmol/L)	−0.007	0.921
Cr (μmol/L)	−0.100	0.153
UA (μmol/L)	0.175	0.061
ALT (IU/L)	0.094	0.182
AST (IU/L)	0.019	0.921

n = 212. 2hPG, 2-h postprandial glucose; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; Cr, serum creatinine; DBP, diastolic blood pressure; FIns, fasting plasma insulin; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL-c, high density lipoprotein cholesterol; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-c, low density lipoprotein cholesterol; MetC, metabolic components; SBP, systolic blood; TC, total cholesterol; TG, triglyceride; UA, serum uric acid.

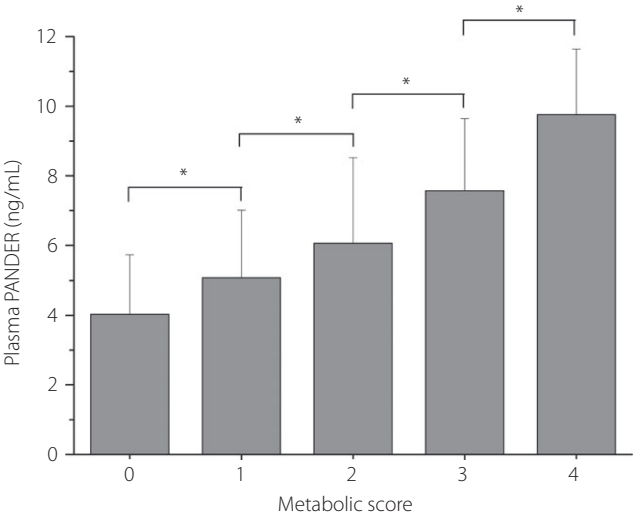

Figure 1 | Plasma pancreatic-derived factor (PANDER) levels elevated with increasing number of metabolic syndrome components. The histogram shows the plasma PANDER (ng/mL); 0, 1, 2, 3, 4 shows the metabolic score. Metabolic score is the number of metabolic syndrome components: abdominal obesity, hypertension, dyslipidemia (high triglyceride and/or low high-density lipoprotein cholesterol) and hyperglycemia. Metabolic score 0 (*n* = 68), metabolic score 1 (*n* = 68), metabolic score 2 (*n* = 45), metabolic score 3 (*n* = 17), metabolic score 4 (*n* = 14). *$P < 0.05$.

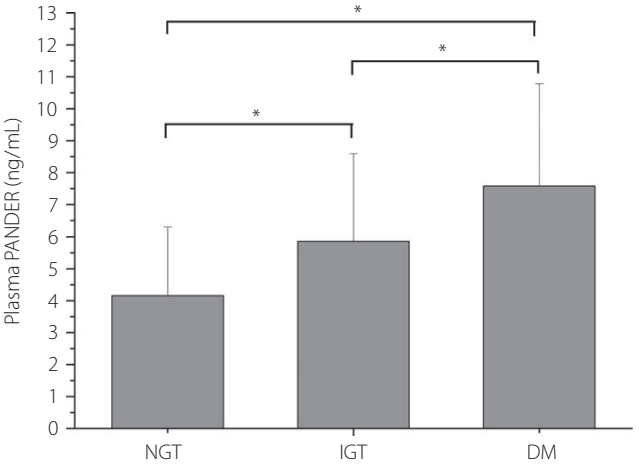

Figure 2 | Plasma pancreatic-derived factor (PANDER; ng/mL) in participants with normal glucose tolerance (NGT; *n* = 149), impaired glucose tolerance (IGT; *n* = 40) and diabetes mellitus (DM; *n* = 23). *$P < 0.05$.

BMI, waist circumference, plasma insulin, HOMA-IR and blood pressure.

In previous studies, it was reported that PANDER induced the apoptosis of islets[17,18], which might be one reason why there was a negative correlation between circulating PANDER and HOMA-β in the present study. Wilson *et al.*[25] reported that high circulating PANDER levels induced fasting hyperglycemia in mice as a result of PANDER promoting hepatic glucose production during fasting. Subsequently, fasting hyperglycemia could result in unusually high postprandial glucose[27]. As expected, the present data showed that elevated FPG and 2hPG were positively correlated with increasing plasma PANDER. Based on the aforementioned observations, it is thus possible that high levels of PANDER could show predictive information for hyperglycemia.

Obesity can lead to systemic insulin resistance by low-grade chronic inflammation in adipose tissue, liver and skeletal muscle[28–30]. According to previous literature, PANDER and insulin were co-secreting[15,16], and knockdown of PANDER significantly attenuated insulin resistance[22]. Unfortunately, the present results showed that there were no significant associations of circulating PANDER with HOMA-IR. As most of the enrolled participants in the study were not overweight or obese, it was proposed that PANDER seemed to be more related to pancreatic β-cell function, as shown by HOMA-β, rather than insulin resistance in normal weight participants.

Table 3 | Association of pancreatic-derived factor with the presence of impaired glucose tolerance: logistic regression analyses

	PANDER (ng/mL)	OR (95% CI)	*P*-value
First quartile	<3.26	1	1
Second quartile	3.26–5.13	1.15 (0.41–3.25)	0.791
Third quartile	5.13–7.43	1.65 (0.61–4.43)	0.323
Fourth quartile	>7.43	3.41 (1.34–8.68)	0.010

CI, confidence interval; OR, odds ratio; PANDER, pancreatic-derived factor.

In the present study, we found that plasma PANDER was associated with dyslipidemia (high TG level and low HDL-c). We speculate that the association of PANDER with higher triglyceride level might be secondary to increased hepatic synthesis of triglycerides by increasing FOXO1 activity[22], and the correlation of PANDER with low HDL-c level might be the result of HDL-c being degraded by hepatic lipase, which is activated in the state of hyperglycemia[31].

Recent studies have shown that PANDER is involved in the potential progression of type 2 diabetes mellitus[32]. Type 2 diabetes mellitus is characterized by a progressive loss of glucose tolerance over several years. Before the development of diabetes, many prediabetic patients present with impaired fasting glucose and/or IGT[33], which are both risk factors for the development of type 2 diabetes mellitus[34]. To assess whether circulating PANDER was independently associated with IGT or diabetes mellitus, we constructed multivariable logistic regression models. Our data showed that the high circulating level of PANDER was significantly associated with a higher OR of onset of IGT or diabetes mellitus. Increased glycemic and insulin levels along with potential hyperlipidemia were the main hallmarks of type 2 diabetes mellitus. Concordantly, recent studies have shown that both glucose and insulin have been identified to stimulate PANDER secretion from pancreatic β-cells[15,16]. In other words, the significance of PANDER was a subsequently result of the induction of increased glycemic and insulin levels during progression of type 2 diabetes mellitus. Therefore, not only might therapeutic intervention of PANDER action decrease glycemic levels, but it also might inhibit the further progression of type 2 diabetes.

We must be cautious during interpretation of our present findings because of the following limitations. First, the main limitation of our study was the uncertainty about the sequence among plasma PANDER and MetS and/or IGT because of the cross-sectional design. Therefore, the results should be confirmed in future prospective cohort and interventional studies. Another limitation was that most of the participants recruited into this study were non-obese adults, which could prevent us from finding the association between PANDER and obesity or insulin resistance. More future work will be required to determine the causal effects of PANDER on the development of MetS and diabetes.

In summary, the present study found that elevated circulating PANDER was associated with accumulations of MetS components and the presence of IGT or diabetes mellitus. Circulating PANDER might be a novel biomarker associated with an increased risk of MetS, and further studies are warranted to assess its utility as a predictor of incident MetS.

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DISCLOSURE

The authors declare no conflict of interest.

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