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ORIGINAL RESEARCH

Relationships of pancreatic beta-cell function with microalbuminuria and glomerular filtration rate in middle-aged and elderly population without type 2 diabetes mellitus: a Chinese community-based analysis

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Background: Relationships of pancreatic beta-cell function abnormality with microalbuminuria (MA) and glomerular filtration rate (GFR) may differ by age, ethnicity and accompanied diseases. Previous studies were generally conducted in Western adult patients with type 2 diabetes mellitus (T2DM), and it is uncertain whether pancreatic beta-cell function is associated with MA and GFR in Chinese community-dwelling middle-aged and elderly population without T2DM. We therefore examined the relationships of pancreatic beta-cell function with two indices of renal damage, MA and GFR, in Chinese community-dwelling middle-aged and elderly population without T2DM.

Methods: This analysis focused on 380 Beijing residents older than 45 years who were free of T2DM and completed the evaluation of pancreatic beta-cell function.

Results: Median age was 67 (49–80) years. Levels of triglyceride, diastolic blood pressure and homeostasis model assessment-beta (HOMA-beta) index were positively related to urine microalbumin ($P<0.05$ for all). Age, low-density lipoprotein cholesterol levels and HOMA-beta index were inversely correlated with GFR, while high-density lipoprotein cholesterol levels were positively correlated with GFR ($P<0.05$ for all). In all three adjustment models, there was a significant positive association between HOMA-beta index and MA; subjects with higher beta-cell function had higher odds of MA ($P<0.05$ for all). There was no association between HOMA-beta index and GFR <60 mL/min/1.73 m^2 in any model ($P>0.05$ for all).

Conclusion: Modeling the pancreatic beta-cell function with different adjusted variables provided the same conclusion of association with MA; beta-cell function was positively associated with MA. Additionally, there was a specific difference in the adjusted associations of pancreatic beta-cell function with MA and GFR <60 mL/min/1.73 m^2; beta-cell function was not independently associated with GFR <60 mL/min/1.73 m^2. This result indicated that abnormal pancreatic beta-cell function plays an important role in the development of MA.

Keywords: pancreatic beta-cell function, microalbuminuria, glomerular filtration rate, Chinese community-dwelling population, middle-aged and elderly

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Background

The primary defects observed in type 2 diabetes mellitus (T2DM) are developed insulin resistance and abnormal insulin secretion by pancreatic beta-cells.[1] Insulin sensitivity and beta-cell function may have independent relationships to microvascular

and macrovascular complications. Although macrovascular complications account for the majority of excess mortality in T2DM, microvascular complications are a significant cause of morbidity. Microvascular damage to the renal glomerulus leads to diabetic nephropathy, a significant cause of renal failure.[2] Early change of vascular permeability manifests clinically as microalbuminuria (MA), which is now accepted as a marker of systemic endothelial dysfunction.[3] A total of 30%–40% of patients with T2DM develop MA, which in 5%–10% of patients may already be present at the diagnosis of T2DM.[4–6] Every year, 2%–5% of those with normal urinary albumin excretion develop MA, 2%–3% of those with MA progress to macroalbuminuria, and 2%–3% of those with macroalbuminuria progress to declined glomerular filtration rate (GFR) that may ultimately require dialysis or transplantation.[6–9] Persistent MA increases the risk for end-stage renal disease two- to four-fold.[10] Data on the relationships of pancreatic beta-cell abnormality with MA and GFR are less clear in adults with T2DM, because such relationships have been suggested by some studies but have not been confirmed by others.[11–16] Moreover, previous studies were generally conducted in adults with T2DM, and it is uncertain whether beta-cell function is associated with MA and GFR in middle-aged and elderly population without T2DM. Relationships between pancreatic beta-cell function abnormality and renal damage may differ by age, ethnicity and accompanied diseases, and it is also unclear whether pancreatic beta-cell function is closely linked to MA and GFR in Chinese community-dwelling population. In this study, we therefore examined the relationships of pancreatic beta-cell function with two indices of renal damage, MA and GFR, in Chinese community-dwelling population older than 45 years who had no clinical diagnosis of T2DM.

Methods

This study was approved by the Ethics Committee of Chinese People's Liberation Army General Hospital (Beijing, People's Republic of China). Each subject provided written informed consent. For a general health check-up in Beijing, 476 participants >45 years of age were recruited between May 2007 and July 2009. A total of 96 participants with T2DM diagnosis, defined as fasting blood glucose (FBG) ≥7.0 mmol/L or receiving oral hypoglycemic agents or insulin, were removed from the analysis. Eventually, this analysis focused on 380 participants who were free of confounding clinical T2DM and completed the evaluation of pancreatic beta-cell function. Blood pressure measurements were undertaken twice with at least 1-minute interval using a mercury sphygmomanometer in a standardized manner; cuff size was adjusted to the circumference of the arm. Mean of two blood pressure measurements was then calculated. Subjects were instructed to fast overnight. A vein blood sample was collected in a tube between 8 am and 10 am and routinely maintained until assayed by well-trained personnel blinded to clinical data, who belonged to the central laboratory in the Department of Biochemistry, on the same day. FBG, triglyceride and high-density lipoprotein cholesterol (HDL-c) were measured directly by a qualified technician blinded to clinical data using enzymatic assays (Roche Products Ltd., Basel, Switzerland) on a common clinical autoanalyzer (COBAS 6000; Roche Products Ltd), and low-density lipoprotein cholesterol (LDL-c) was calculated. Fasting insulin (FINS) levels were determined by DPC kit (DPC Cirrus Inc., Los Angeles, CA, USA) on a fully automatic chemiluminescence analyzer (DPC IMMULITE 1000; DPC Cirrus Inc.). As a measure of pancreatic beta-cell function, we calculated the homeostasis model assessment-beta (HOMA-beta) index using the following formula (with glucose and insulin levels as indicated earlier): HOMA-beta = 20× FINS (mU/L)/[FBG (mmol/L) − 3.5].[17] MA was defined as urine microalbumin (UMA) of 30–299 mg/L. Serum creatinine levels were measured by enzymatic assay (Roche Diagnostics GmbH) on a Hitachi 7600 autoanalyzer (Hitachi, Tokyo, Japan). GFR was calculated from serum creatinine using the Chinese modified modification of diet in renal disease equation: 175× serum creatinine $(mg/dL)^{-1.234}$ × age $(years)^{-0.179}$ ×0.79 (if female).[18]

Statistical analysis

Data are reported as mean (standard deviation) for continuous variables with normal distribution, median (interquartile range) for continuous variables with abnormal distribution and proportions for categorical variables. We tested the difference in subjects with and without MA and GFR <60 mL/min/1.73 m^2 using Student's *t*-test for continuous variables with normal distribution, Mann–Whitney *U*-test for continuous variables that were not normally distributed or χ^2 analysis for categorical variables. We evaluated simple relationships of different parameters with MA and GFR <60 mL/min/1.73 m^2 using Pearson (normal distribution) and Spearman (skewed distribution) coefficients. We performed logistic regression in the models, adjusting for potential confounders, including model 1 (no adjustment), model 2 (age and sex), and model 3 (model 2 plus systolic blood pressure [SBP], diastolic blood pressure [DBP], triglyceride, HDL-c and LDL-c) and reported multivariable-adjusted associations for beta-cell function with the presence of MA and GFR <60 mL/min/1.73 m^2. Two-tailed

Table 1 Characteristics of study population grouped in participants with and without MA or GFR <60 mL/min/1.73 m^2

Variables	UMA			GFR		
	Normal UMA (n=303)	MA (n=77)	*P*-value	Normal GFR (n=303)	GFR <60 mL/min/1.73 m^2 (n=77)	*P*-value
Age (years)	67 (61–71)	66 (66–71)	0.452	66 (61–71)	71 (66–73)	0.065
Males (%)	110 (36.3)	44 (57.1)	<0.001	110 (36.3)	44 (57.1)	<0.001
SBP (mmHg)	130 (120–143)	145 (135–149)	0.023	131 (121–144)	125 (120–130)	0.327
DBP (mmHg)	75 (69–82)	81 (70–86)	0.244	75 (69–82)	76 (65–78)	0.298
Triglyceride (mmol/L)	1.56 (1.17–2.06)	1.75 (1.31–3.93)	0.304	1.56 (1.17–2.04)	1.78 (1.35–2.62)	0.406
HDL-c (mmol/L)	1.33 (1.07–1.64)	1.19 (1.18–1.60)	0.947	1.33 (1.09–1.64)	1.08 (0.87–1.34)	0.058
LDL-c (mmol/L)	3.07 (2.58–3.64)	3.09 (2.41–4.10)	0.844	3.07 (2.57–3.64)	3.01 (2.56–4.39)	0.528
FBG (mmol/L)	4.84 (4.40–5.54)	4.43 (4.01–5.11)	0.211	4.81 (4.38–5.50)	6.01 (4.50–6.10)	0.211
FINS (mU/L)	7.42 (4.88–10.16)	10.72 (6.35–12.18)	0.259	7.48 (4.93–10.24)	6.62 (4.56–16.28)	0.849
HOMA-beta	105.21 (69.91–170.74)	157.76 (89.27–477.65)	0.109	105.21 (70.06–174.65)	109.42 (82.39–136.36)	0.722
Dependent variables						
UMA (mg/L)	0.74 (0.39–1.59)	47.00 (41.90–74.00)	<0.001	0.77 (0.40–1.65)	0.71 (0.47–4.24)	0.728
GFR (mL/min/1.73 m^2)	82.58 (75.47–89.37)	74.23 (66.20–85.66)	0.123	82.81 (75.87–89.47)	55.73 (46.96–57.32)	<0.001

Note: Data presented as median (interquartile range).
Abbreviations: MA, microalbuminuria; GFR, glomerular filtration rate; UMA, urine microalbumin; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FBG, fasting blood glucose; FINS, fasting insulin; HOMA, homeostasis model assessment.

$P<0.05$ was considered as statistically significant. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 17 software (SPSS Inc., Chicago, IL, USA).

Results

Median age of all participants was 67 (49–80) years, and 40.5% were male. As shown in Table 1, subjects with MA had significantly higher SBP ($P<0.05$) and moderately higher HOMA-beta index ($P=0.109$), compared with subjects without MA. Compared with subjects without GFR <60 mL/min/1.73 m^2, subjects with GFR <60 mL/min/1.73 m^2 had moderately higher age ($P=0.065$) with moderately lower HDL-c ($P=0.058$) but without higher HOMA-beta index ($P>0.05$).

Table 2 Bivariate correlations with UMA and GFR in the whole cohort

Variables	UMA		GFR	
	Correlation coefficients	*P*-value	Correlation coefficients	*P*-value
Age (years)	0.045	0.432	–0.336	<0.001
Females (%)	0.068	0.234	0.094	0.097
SBP (mmHg)	0.048	0.401	–0.090	0.115
DBP (mmHg)	0.121	0.033	–0.013	0.824
Triglyceride (mmol/L)	0.224	<0.001	–0.106	0.064
HDL-c (mmol/L)	0.017	0.768	0.299	<0.001
LDL-c (mmol/L)	0.013	0.824	–0.112	0.049
HOMA-beta	0.244	<0.001	–0.121	0.033

Abbreviations: UMA, urine microalbumin; GFR, glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; HOMA, homeostasis model assessment.

Table 2 shows that the levels of triglyceride, DBP and HOMA-beta index were positively related to UMA ($P<0.05$ for all). Age, LDL-c levels and HOMA-beta index were inversely correlated with GFR, while HDL-c levels were positively correlated with GFR ($P<0.05$ for all). In all three models (Table 3), there was a significant positive association between HOMA-beta index and MA; subjects with higher pancreatic beta-cell function had higher odds of MA ($P<0.05$ for all). There was no association between HOMA-beta index and GFR <60 mL/min/1.73 m^2 in any model ($P>0.05$ for all).

Discussion

There is an international consensus that diabetic nephropathy is a leading cause of renal damage in developed countries and also occupies a pivotal position as a cause of renal damage in developing countries.[2] It is preceded by MA, which typically progresses to proteinuria and reduced GFR when left untreated.[4–10] Early change of vascular permeability manifests clinically as MA, which is now accepted as a marker of systemic endothelial dysfunction.[3] T2DM is characterized by both abnormal beta-cell function and impaired insulin sensitivity.[1] Relationships of pancreatic beta-cell abnormality with MA and GFR have not been well studied.[11] Studies regarding the relationships of pancreatic beta-cell function with MA and GFR were mainly performed in adults with T2DM, and additional investigation is needed to determine whether pancreatic beta-cell function has similarities in their relationships with MA and GFR in middle-aged and elderly population without T2DM. Thus, we excluded the patients with clinical T2DM in our analysis. Moreover, to study whether ethnicity may affect the relationships of pancreatic

Table 3 Associations of HOMA-beta with MA and GFR <60 mL/min/1.73 m^2 according to multivariate analysis

Models	MA		GFR <60 mL/min/1.73 m^2	
	OR value (95% CI)	*P*-value	OR value (95% CI)	*P*-value
First model	1.004 (1.000–1.008)	0.030	0.999 (0.996–1.002)	0.603
Second model	1.005 (1.001–1.009)	0.020	0.999 (0.996–1.002)	0.540
Third model	1.006 (1.001–1.011)	0.014	0.998 (0.995–1.002)	0.302

Notes: First model: no adjustment; second model: regression model adjusted by age and gender; third model: regression model adjusted by age, gender, SBP, DBP, triglyceride, HDL-c and LDL-c.

Abbreviations: HOMA, homeostasis model assessment; MA, microalbuminuria; GFR, glomerular filtration rate; OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

beta-cell function with MA and GFR, there is particularly a concern for these relationships in Chinese community-dwelling population due to a lack of similar studies. Unlike previous studies, our study sample included a representation of Chinese community-dwelling population, a historically understudied population. In addition, we selected the HOMA-beta index for analysis based on its performance in previous investigations and its utility in population-based studies.[11] HOMA-beta index as a measure of pancreatic beta-cell function relies on basal insulin secretion and hepatic glucose production, and hence it is practical for application in clinical and epidemiological settings. Therefore, we believed that HOMA-beta index could work as a reliable indicator of pancreatic beta-cell function.

In adults with T2DM, previous studies have yielded inconsistent results as to whether there is a relationship between pancreatic beta-cell function and MA. Some studies have found a relationship,[12,13] whereas others have not.[14–16] In the Framingham Offspring Study, participants with hyperinsulinemia tended to have a greater proportion of MA than those without hyperinsulinemia.[19] In a healthy middle-aged population, reduced insulin sensitivity is continuously related to a greater risk of increasing albuminuria.[20] In this analysis, the association between pancreatic beta-cell function and MA remained significant after controlling for different confounders. This finding demonstrated that abnormal beta-cell function either was obviously related to or causally contributed to the initial pathogenesis of albuminuria. Impaired signaling at the receptor level leads to the signaling pathway defects, as seen in insulin resistance, and results in a compensatory hyperinsulinemia.[21] Hyperinsulinemia leads to the hypercoagulability, inflammation, fibrinolysis, endothelial dysfunction and oxidative stress and results in an increased risk of MA.[21] Recent evidence has supported that hyperinsulinemia is a significant modulator of filtration barrier function and responsible for the presence of MA through the components of insulin-signaling pathways, such as glucose transporter-4, insulin receptor substrate-1 and -2, vesicular snare, and vesicle-associated membrane components in the podocyte.[3] In addition, hyperinsulinemia can contribute to the mesangial and interstitial remodeling that may further promote the development of MA.[22] Furthermore, insulin contributes to the development of MA by affecting the transforming growth factor beta production in the mesangium and proximal tubule cells, which has been shown to increase the fibrosis in the interstitium and podocyte remodeling.[23,24] Finally, several inflammatory factors, such as free fatty acid, adiponectin, leptin, resistin, tumor necrosis factor α and interleukin-6, mediate the relationship between insulin resistance/hyperinsulinemia and MA.[25–27]

Conversely, the association between pancreatic beta-cell function and GFR <60 mL/min/1.73 m^2 did not reach statistical significance after adjusting for different variables in this analysis. The presence or absence of this association seems to arise from a difference in pancreatic beta-cell function status of subjects. We supposed that in subjects without T2DM, the association between pancreatic beta-cell function and progressive loss of renal function has not been thoroughly expressed, because T2DM (or greater degree of abnormal beta-cell function) may provide a fundamental milieu for the association between beta-cell function and GFR.

Conclusion

In this analysis, modeling the pancreatic beta-cell function with different adjusted variables provided the same conclusion of association with the presence of MA; beta-cell function was positively associated with MA. In addition, there was a specific difference in the adjusted associations of pancreatic beta-cell function with MA and GFR <60 mL/min/1.73 m^2; beta-cell function was not independently associated with GFR <60 mL/min/1.73 m^2. This result indicated that abnormal pancreatic beta-cell function plays an important role in the development of MA.

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Disclosure

The authors report no conflicts of interest in this work.

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