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Original article

Metabolic syndrome, but not insulin resistance, is associated with an increased risk of renal function decline

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SUMMARY

Background & aims: The purpose of this study was to evaluate the effect of metabolic syndrome (Mets) and insulin resistance (IR) on the risk of renal function decline (RFD) in a rural Chinese cohort.
Methods: A total of 2696 subjects aged 40–71 years with normal renal function were followed-up for 7 years. RFD was defined using the Kidney Disease: Improving Global Outcome definition, i.e., a drop in estimated glomerular filtration rate (eGFR) category accompanied by a 25% or greater drop in eGFR from baseline or a sustained decline in eGFR of more than 5 mL/min/1.73 m^2/year.
Results: During the 7-year follow-up, 9.0% of the subjects developed RFD. Subjects with Mets at baseline had an increased risk of RFD with an adjusted odds ratio (OR) of 1.77 (95%CI: 1.25–2.52), and there was a graded relationship between the numbers of Mets components and the risk for RFD. Exclusion of the subjects with hypertension (1.65; 0.99–2.75) or diabetes (1.86; 1.30–2.67) at baseline or further adjustment for IR (1.72; 1.15–2.57) did not substantially change the association between Mets and the risk of RFD. Moreover, the ORs of Mets status for RFD in the older group (≥55 years) were 2.14 (1.06–4.33) times of that in the younger group (<55 years) and 2.26 (1.07–4.78) times in hypercholesterolemia group (≥5.2 mmol/L) of that in the normal (<5.2 mmol/L) group. The baseline IR was not associated with the risk for RFD.
Conclusions: Mets, but not IR, was associated with an increased risk for RFD. And there was a detrimental interaction of Mets with older age and hypercholesterolemia on the risk of RFD.

1. Introduction

Chronic kidney disease (CKD) substantially elevates the risk of cardiovascular diseases, end-stage renal disease (ESRD) and other complications, and is now recognized as a worldwide public health problem [1]. A recent national cross-sectional survey [2] showed that the overall prevalence of CKD in adult Chinese was 10.8% (10.2–11.3); and the prevalence was higher in rural (11.3% [10.6–12.0]) than in urban areas (8.9% [8.2–9.6]); furthermore, economic development was independently associated with the presence of albuminuria in rural areas only. These findings indicate that CKD has become an important public health problem in China, and special attention should be paid to residents in economically improving rural areas. Furthermore, even mild decline of renal function is associated with an increased risk for CVD and mortality [3,4]. A better understanding of the modifiable risk factors of renal function decline (RFD) in apparently healthy population, leading to early detection and prevention, might alleviate the future burden of CKD and associated complications.

Metabolic syndrome (Mets), characterized by a cluster of abdominal obesity, elevated blood pressure, dyslipidemia (elevated triglycerides and low high-density lipoprotein cholesterol), and elevated fasting glucose, is associated with an increased risk for diabetes, cardiovascular disease, as well as cardiovascular death and all-cause mortality [5]. A central feature

Abbreviations: CKD, Chronic kidney disease; eGFR, estimated glomerular filtration rate; IR, insulin resistance; Mets, Metabolic syndrome; RFD, renal function decline.

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of Mets is insulin resistance (IR), although the pathogenesis remains unclear. Due to the economic development and consequential changes in lifestyle and diet, Mets has also become increasingly common in China [6]. A national cross-sectional survey in 2000–2001 indicated that 64 million (or 13.7%) adults aged 35–74 years in China had Mets [7].

Previous studies in various ethnic populations have suggested that Mets is associated with an increased risk for CKD [8–12], as well as kidney stones [13]. However, CKD and RFD may not completely share the common risk factors [11], and prospective studies investigating the association between Mets and RFD were limited, particularly in healthy populations. Therefore, in the current study, we aimed to evaluate the effect of Mets and IR on the risk of RFD in a rural Chinese cohort with normal renal function (estimated glomerular filtration rate (eGFR) value of ≥60 mL/min/1.73 m^2), and to identify possible effect modifiers. Besides the RFD outcome, we also included rapid eGFR decline, defined as a decline of eGFR of greater than 3 mL/min/1.73 m^2/year [11], and incident CKD, defined as an eGFR below 60 mL/min/1.73 m^2, as the secondary outcomes in our analyses.

2. Materials and methods

2.1. Study population

Study participants were from an epidemiological study of Mets conducted during 2003–2005 in rural communities in Anqing, Anhui province of China. Detailed protocol of the study was described previously [14]. In 2011, 6301 of the study subjects were invited for a follow-up visit, and 2901 (46%) of them responded. The non-responders did not differ substantially with respect to baseline characteristics compared with the responders (data not shown). This study was approved by the Institutional Review Boards from the Nanfang Hospital in Guangzhou and the Institute of Biomedicine in the Anhui Medical University. Written informed consent was obtained from each study participant.

2.2. Data collection

Baseline data including questionnaires on sociodemographic status, occupation, diet, lifestyle, health behavior, and medical history, blood pressure and anthropometric measurements, as well as blood tests was collected by trained research staff according to protocols described previously [14]. Physical activity level was self-reported as mild, moderate, and heavy.

Venous blood was drawn from the forearm of each participant in the fasting status. Serum and plasma were separated from blood cells in the field within 30 min and kept frozen at −20 °C. Serum creatinine concentrations were determined using an enzymatic method (sarcosine oxidase-PAP). Fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) were measured on the Hitachi 7020 Automatic Analyzer. Plasma insulin was measured by using an enhanced chemiluminescence method on an Elecsys 2010 system (Roche, Basel, Switzerland).

The insulin resistance index of homeostasis model assessment (HOMA-IR) was calculated from the fasting concentrations of insulin and glucose using the formula: fasting serum insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5 [15]. Within the cohort, we measured HOMA-IR in 2359 non-diabetic subjects.

GFR was estimated using the following equation according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [16]:

$$\mathrm{eGFR} = 141 \times \min(\mathrm{Scr}/\kappa, 1)^{\alpha} \times \max(\mathrm{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\mathrm{Age}} \times 1.018 \ [\text{if female}]$$

where Scr is serum creatinine [mg/dL], κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. GFR was also estimated using the four-component Modification of Diet in Renal Disease (MDRD) equation incorporating age, race, sex and serum creatinine level [17]: $\mathrm{GFR} = 186 \times \mathrm{Scr[mg/L]}^{-1.154} \times \mathrm{age[year]}^{-0.203} \times 0.742$ [if female].

2.3. Definition of metabolic syndrome

The Mets was defined according to the recent harmonized criterion [18] set by the NHLBI/AHA (National Heart, Lung and Blood Institute/American Heart Association) and IDF (International Diabetes Federation) as the presence of three or more of the following conditions: (1) abdominal obesity (WC ≥ 90 cm in men or ≥80 cm in women); (2) elevated TG (≥1.7 mmol/L); (3) low HDL-C (<1.0 mmol/L in men or <1.3 mmol/L in women); (4) elevated blood pressure (SBP ≥ 130 mmHg or DBP ≥ 85 mmHg, or self-reported diagnosis of hypertension); and (5) elevated FPG (≥5.6 mmol/L or self-reported diagnosis of diabetes). In this study, data were also analyzed when abdominal obesity was defined as WC ≥ 80 cm in both men and women according to the criterion suitable for Chinese population [19]. Meanwhile, Mets was defined based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) criterion modified for Asian population [20] and the IDF criterion [21]. The modified NCEP ATP-III criterion for Mets included components the same as in the NHLBI/AHA/IDF definition above except that abdominal obesity was defined as WC > 90 cm in men or >80 cm in women and elevated FPG was defined as FPG ≥ 6.1 mmol/L or self-reported diagnosis of diabetes. And the IDF criterion for Mets required the presence of abdominal obesity plus two of the components included in the NHLBI/AHA/IDF definition above.

2.4. Outcomes

The primary outcome of interest was RFD, which was defined according to the Kidney Disease: Improving Global Outcome (KDIGO) 2012 [22] as follows: a drop in GFR category (≥90 [G1], 60–89 [G2], 45–59 [G3a], 30–44 [G3b], 15–29 [G4], <15 [G5] mL/min/1.73 m^2) accompanied by a 25% or greater drop in eGFR from baseline or a sustained decline in eGFR of more than 5 mL/min/1.73 m^2/year. The decline in eGFR was calculated as (eGFR at baseline − eGFR at revisit)/follow-up year.

The secondary outcomes of interest were rapid eGFR decline, defined as a decline in eGFR of greater than 3 mL/min/1.73 m^2/year [11], and new incidence of CKD, defined as an eGFR at revisit below 60 mL/min/1.73 m^2.

2.5. Statistical analysis

Current smoking was defined as having smoked ≥10 packs in the last year. Current drinking was defined as drinking alcohol at least 1 time per week in the last year. Obesity was defined as BMI ≥ 24 kg/m^2 according to the Working Group on Obesity in China [23]. Hypercholesterolemia was defined as TC ≥ 5.2 mmol/L. Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or self-reported diagnosis of hypertension. Diabetes was defined as fasting glucose ≥ 7.0 mmol/L or self-reported diagnosis of diabetes.

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