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The number of metabolic syndrome components is a good risk indicator for both early- and late-stage kidney damage

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Abstract *Background and aims:* Renal hyperfiltration (early-stage kidney damage) and hypofiltration (late-stage kidney damage) are common in populations at high risk of chronic kidney disease. This study investigated the associations of renal hyperfiltration and hypofiltration with the number of metabolic syndrome (MetS) components.
Methods and results: The study subjects included 205 382 people aged 40–74 years who underwent Specific Health Checkups in Aichi Prefecture, Japan. The prevalence of renal hyperfiltration [estimated glomerular filtration rate (eGFR) above the age-/sex-specific 95th percentile] and hypofiltration (eGFR below the 5th percentile) was compared according to the number of MetS components. We found that the prevalence of both hyperfiltration and hypofiltration increased with increasing number of MetS components (odds ratios for hyperfiltration: 1.20, 1.40, 1.42, 1.41, and 1.77; odds ratios for hypofiltration: 1.07, 1.25, 1.57, 1.89, and 2.21 for one, two, three, four, and five components, respectively, compared with no MetS components). These associations were observed in both normal weight [body mass index (BMI) < 25 kg/m^2] and overweight (BMI ≥ 25 kg/m^2) subjects. Renal hyperfiltration was associated with prehypertension and prediabetes, while hypofiltration was associated with dyslipidemia, abdominal obesity, overt hypertension, and overt diabetes.
Conclusion: The number of MetS components is a good risk indicator of early- and late-stage kidney damage. Therefore, kidney function should be monitored in subjects with MetS components. MetS components should be treated as early as possible to prevent the development of kidney damage and cardiovascular diseases in people with hyperfiltration, regardless of their body weight.

Introduction

Metabolic syndrome (MetS) is a complex of interrelated risk factors for cardiovascular diseases [1]. Recent studies have demonstrated that MetS increases the risk of cardiovascular diseases (CVD) and of chronic kidney disease (CKD) [2,3] as a result of atherosclerotic vascular damage [4]. CKD itself is also an independent determinant of atherosclerotic diseases [5]. Among MetS components, prediabetes, defined as impaired fasting glucose or impaired glucose tolerance [6], and prehypertension [7] were reported to be risk factors for the development of CKD [8,9]. Other MetS components, including dyslipidemia and abdominal obesity, are established risk factors for CKD [10,11].

Glomerular hyperfiltration, or an increased glomerular filtration rate (GFR), is an early and reversible stage of

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kidney damage in subjects with diabetes and hypertension, and is a marker for subsequent progression of nephropathy [12,13]. Recently, we and other researchers have reported that hyperfiltration is very common in people with prediabetes and prehypertension in several ethnic populations [14–16]. A recent review focused on the theme that glomerular hyperfiltration is a marker for early renal damage in prediabetes and prehypertension [17]. Obesity was also reported to be associated with hyperfiltration [18]. Therefore, identifying subjects at an increased risk of nephropathy, among those with MetS components, may offer an important and effective preventive strategy. However, there are limited data showing associations between hyperfiltration and MetS. To our knowledge, only one study has demonstrated that hyperfiltration was associated with MetS components in young males [19], but this association has not been evaluated in the general population.

Weight reduction is the primary treatment of MetS [20]. Because MetS is strongly associated with body weight, the risk of kidney damage among MetS subjects might differ between normal weight and overweight subjects. Therefore, it is important to determine whether the risk of kidney damage attributable to MetS (or its components) in normal weight subjects is similar to that in overweight subjects.

From this context, the purposes of this study were to (1) confirm the associations of hyperfiltration with prediabetes and prehypertension in a large population, (2) reveal the associations of hyperfiltration/hypofiltration with MetS and its other components (i.e., dyslipidemia and abdominal obesity), and (3) compare the associations of hyperfiltration/hypofiltration with MetS between normal weight and overweight subjects.

Methods

Study population

The subjects were people who underwent Specific Health Checkups and Health Guidance (Tokutei-Kenshin) between April 2008 and March 2009 in Aichi Prefecture, Japan. This program was started by the Japanese government in 2008 to facilitate early diagnosis and intervention of MetS [21]. The target population comprises Japanese citizens aged 40–74 years. The present study included subjects with complete data for serum creatinine (SCr) and the following MetS-related parameters [1]: systolic and diastolic blood pressure (BP), fasting plasma glucose (FPG) or hemoglobin A1c (HbA1c), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and waist circumference (WC). Either FPG or HbA1c was measured as an index of glycemic control in this health checkup program according to the guidelines for this program proposed by the Japanese government; therefore, FPG was unknown for approximately half of the subjects. Subjects with a history of cardiovascular or cerebrovascular diseases, and those receiving renal replacement therapy were excluded from this study.

All of the subjects completed a self-administered questionnaire to document their current medications for hypertension, diabetes, and hyperlipidemia, history of cardiovascular and cerebrovascular diseases, and smoking habits (current smoker or not). BP measurement, and blood (after fasting for >8 h) and urine sampling were performed at each medical institution. HbA1c values are presented in National Glycohemoglobin Standardization Program (NGSP) units, which were calculated with the following equation: HbA1c (NGSP, %) = 1.02 × HbA1c (Japan Diabetes Society, %) + 0.25%.

This study was conducted by the Aichi CKD Epidemiology Conference with support from the Aichi Kidney Foundation. This study was approved by the Ethics Committee of Nagoya University School of Medicine (approval number 679).

Definitions of MetS components and MetS

Subjects were categorized as having normal BP (i.e., no prehypertension; BP < 120/80 mmHg), stage 1 prehypertension (BP 120–129/80–84 mmHg), stage 2 prehypertension (BP 130–139/85–89 mmHg), or hypertension (BP ≥ 140/90 mmHg or the use of antihypertensive drugs) [8]. Subjects were also categorized as having normal fasting glucose (i.e., no prediabetes; FPG < 100 mg/dL), stage 1 prediabetes (FPG 100–109 mg/dL), stage 2 prediabetes (FPG 110–125 mg/dL), or diabetes (FPG ≥ 126 mg/dL or the use of glucose-lowering drugs) [6]. Based on HbA1c levels, subjects were categorized as having no prediabetes (HbA1c < 5.7%), stage 1 prediabetes (HbA1c 5.7–6.0%), stage 2 prediabetes (HbA1c 6.1–6.4%), or diabetes (HbA1c ≥ 6.5% or the use of glucose-lowering drugs) [6,22].

The diagnostic criteria for the assessment of MetS components were defined according to the Joint Scientific Statement for harmonizing MetS [1] as follows: elevated BP was defined as BP ≥ 130/85 mmHg or the use of antihypertensive drugs; elevated FPG was defined as FPG ≥100 mg/dL or the use of glucose-lowering drugs; reduced HDL-C was defined as HDL-C <40 mg/dL in men and <50 mg/dL in women, or the use of lipid-lowering drugs; elevated TG was defined as TG ≥ 150 mg/dL or the use of lipid-lowering drugs; and elevated WC was defined as WC ≥ 90 cm in men and ≥80 cm in women for Asians. MetS was defined as the presence of three or more of these five components. Elevated HbA1c (defined as HbA1c ≥ 5.7%) was used as the surrogate marker for glycemic status [22].

Definitions of renal hyperfiltration and hypofiltration

SCr was measured using an enzymatic method in almost all of the laboratories. The GFR was estimated from the SCr value, using the Japanese GFR equation [23], as follows: estimated GFR (eGFR) (mL/min/1.73 m^2) = 194 × $SCr^{-1.094}$ (mg/dL) × $age^{-0.287}$ (years) (×0.739 if female). The reference values for hyperfiltration and hypofiltration were determined in presumably healthy subjects. The distributions of eGFR in subjects with no MetS components (i.e., subjects