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Metabolic syndrome component combinations and chronic kidney disease: The severance cohort study

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ABSTRACT

Objectives: The effects of ethnicity and gender can produce varying results when evaluating risk of chronic kidney disease (CKD) development and metabolic syndrome (MetS) components. The risks of specific MetS component combinations and incident CKD are unclear. The aim of this study was to investigate the relationship between the combination of MetS components and CKD.

Methods: This prospective cohort study included 15,401 participants. Koreans 20–84 years of age were followed for 5.2 years. The NCEP-ATP III definition of MetS was used. CKD was defined as an estimated glomerular filtration rate of <60 ml/min/1.73 m^2 by the simplified Modification of Diet in Renal Disease equation.

Results: The incidence rate per 1000 person-years of CKD was determined in men (13.8) and women (14.1) with MetS. In a multivariate Cox proportional hazard model controlling for age and lifestyle variables, increased CKD risk in men (hazard ratio 1.45, 95% confidence interval 1.20–1.76) and women (1.52, 1.19–1.93) with Mets was found compared to those without MetS. Incidence and HRs for CKD elevated with increasing numbers of MetS components in men and women (*P* for trend <0.0001). The risks associated with MetS varied by combination of causative factors. High blood pressure (BP) and low high-density lipoprotein (HDL) were more likely to be associated with risk of CKD development.

Conclusions: BP and HDL were the leading risk factors for CKD development in healthy Koreans. The association between MetS and kidney dysfunction were significantly independent of traditional cardiovascular risk factors.

1. Introduction

Chronic kidney disease (CKD) is becoming a major global public health concern, and its prevalence and incidence are steadily increasing [1]. CKD is associated with end-stage renal disease (ESRD), cardiovascular disease, all-cause mortality, and premature death [2,3]. Some CKD patients have died prematurely because of cardiovascular disease and renal dysfunction co-morbidity not to renal failure alone [2]. Metabolic syndrome (MetS) and CKD share similar pathogenesis pathways including inflammation, oxidative stress, and dyslipidemia [4,5]. Recently, several studies reported relationships among CKD and others like MetS, microalbuminuria, age, gender and lifestyle factors (alcohol intake, smoking and deficient physical activity) [6–8]. In addition, some cross-sectional studies and cohort studies [6,9–11] have suggested a MetS and CKD association.

MetS is a cluster of characteristics including disturbed glucose and insulin metabolism, being overweight, abdominal fat distribution, hypertension, and dyslipidemia [12]. Recently, the age-adjusted prevalence of MetS in the US from the National Health and Nutrition Examination Survey (NHANES) III and NHANES 1999–2006 was 29.2%–34.3% among adults aged ≥20 years [13]. This increasing trend has also been observed in Koreans from 24.9% (1998) to 31.3% (2007) among adults aged ≥20 years from the Korean National Health and Nutrition Examination Survey from 1998 to 2007 [14].

Many previous studies have shown MetS components lead to increased CKD [6,9–11]. In addition, the combination of MetS risk factors can produce different effects in comparison to an individual

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; NHANES, the National Health and Nutrition Examination Survey; FSG, fasting serum glucose; HDL, high-density lipoprotein; LCAT, lecithin cholesterol acyltransferse; LDL, low-density lipoprotein; MDRD, the simplified Modification of Diet in Renal Disease; MetS, metabolic syndrome; NCEP-ATP III, the National Cholesterol Education Program/Adult Treatment Panel III; PY, person-year; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

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risk factor for CKD. Only a few studies have demonstrated a relationship between MetS component combinations and the incidence of CKD [9,11]. The specific MetS component combinations that relate to CKD are unclear, and which MetS components are strongly predictive in the general Korean population are not known.

Therefore we performed a prospective cohort study to examine the relationships between multiple MetS components and CKD in healthy Koreans.

2. Subjects and methods

2.1. Study subjects

The cohort population consisted of 20,582 Korean men and women aged 20–84 years who participated in at least one medical evaluation at the Severance Health Promotion Center from 1994 to 2004 [15] and followed-up on December 31, 2011. To avoid incidence of CKD due to pre-existing conditions and other confounding factors, we excluded 5181 subjects as follows: past self-reported CVD (n = 94), past history of CKD (n = 27), past history of gout (n = 15), history of medication related to gout (n = 5), those with an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 defined as CKD at baseline or prior to their initial visit (n = 765), missing smoking status and alcohol intake information (n = 4242), and subjects who were lost to follow-up (n = 31). The final study sample included 15,401 subjects. The Institutional Review Board for Human Research of Yonsei University approved of this study.

2.2. Data collection

Subjects were asked to describe their smoking habits (never smoker, ex-smoker, or current smoker) and alcohol consumption (non-drinker or drinker of any amount of alcohol). Other demographic characteristics such as age, sex, and past history of diabetes, hypertension, CKD or gout were obtained from the subjects. Subjects were asked if they participated in regular physical activity and were subsequently divided into an activity or non-activity group. Body weights and heights were measured while participants were wearing light clothing. A registered nurse or technician measured blood pressure using a standard mercury sphygmomanometer while subjects were seated. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured after at least a five minute rest period.

2.3. Measurement of biomarkers

For clinical chemistry assays, serum was separated from peripheral venous blood samples obtained from each participant after 12 h of fasting, and stored at −70 °C for 2 h. Serum creatinine was measured using the kinetic method of the Jaffe reaction. MetS biomarkers such as fasting serum glucose (FSG), total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), and high density lipoprotein (HDL) were measured using a Hitachi-7600 Analyzer (Hitachi Ltd., Tokyo, Japan). All measurements were performed by a central laboratory at Severance Hospital, Yonsei University Health System, Seoul, Korea. Data quality control was maintained in accordance with the procedures of the Korean Association of Laboratory Quality Control.

2.4. Definition of MetS

Subjects with at least three of the following NCEP-ATP III criteria [12] were defined as having MetS: (1) BP ≥130/85 mmHg, (2) FSG ≥110 mg/dL or ≥6.1 mmol/L, (3) serum triglycerides (TG) ≥150 mg/dL or 1.69 mmol/L, (4) HDL cholesterol, 40 mg/dL or <1.03 mmol/L in men and 50 mg/dL or <1.29 mmol/L in women, and (5) body mass index (BMI) ≥25 kg/m^2 (waist measurements were not available). This data set did not have enough measurements of fasting serum insulin for calculating the homoeostasis model assessment insulin resistance (HOMA-IR). So we were able to conduct analysis using NCEP-ATP III (the National Cholesterol Education Program/Adult Treatment Panel III) or IDF (the International Diabetes Federation) but with limited data.

2.5. Assessment of renal function

Renal function was estimated by the simplified Modification of Diet in Renal Disease (MDRD) equation, which determined the eGFR (ml/min/1.73 m^2) = 186 × $P_{Cr}^{-1.154}$ × age$^{-0.203}$ (× 0.742, if female; × 1.212, if black) [16].

Kidney function was divided into Grade 1 (≥90 ml/min/1.73 m^2), Grade 2 (75–89.9 ml/min/1.73 m^2), Grade 3 (60–74.9 ml/min/1.73 m^2), and Grade 4 (<60 ml/min/1.73 m^2) using the calculated eGFR.

2.6. Follow-up and CKD outcome

The main outcome variable was CKD which was defined as an eGFR of <60 ml/min/1.73 m^2. For individuals who had more than one CKD event during the follow-up period from January 1, 1994 to December 31, 2011, only the first event was included in statistical analysis. During 79,698.2 person-years (PYs) of follow-up, 100% of all subjects had more than one measurement at baseline; 44.7% had two or more; 20.9% had three or more; 11.7% had four or more; and 22.7% had over five measurements. Computerized searches for death certificates were performed using the identification number assigned at birth by the National Statistical Office.

Overweight determinations were based on a BMI ≥25 kg/m^2. Additionally, we created a category for diabetes by combining subjects with self-reported treatment for diabetes or with FSG levels ≥126 mg/dL. Hypertension was defined as SBP of at least 140 mmHg, DBP of at least 90 mmHg, or self-reported treatment for hypertension. Dyslipidemia was defined as follows: TG levels ≥200 mg/dL; HDL levels < 40 for men, <50 for women; LDL levels ≥160 mg/dL; total cholesterol (TC) ≥240 mg/dL; and treatment with medicine or past personal history of dyslipidemia.

2.7. Statistical analysis

To examine the association between MetS and eGFR, Cox proportional hazard models were examined after adjusting for age, smoking status, alcohol consumption, and physical activity. Cox proportional hazard models were used to calculate the risk of having CKD (eGFR of <60 ml/min/1.73 m^2) by comparing values for MetS components. All analysis was performed separately for men and women, using SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided, and statistical significance was denoted as P < 0.05.

3. Results

3.1. Cohort characteristics

We performed a prospective study of 15,401 Korean men (8959) and women (6442). The majority of cohort members were middle-aged at baseline. The results show the mean levels for measured MetS components and other risk factors according to eGFR categories. A small percentage of Korean men and women (2.31% and 1.96%, respectively in our data) fell into the BMI ≥30 kg/m^2 criteria used for western populations. In men, age, BMI, TC, HDL, TG, DBP, creatinine, ex-smoker, and physical activity showed