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High-normal albuminuria predicts metabolic syndrome in middle-aged Korean men: A prospective cohort study

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ABSTRACT

Objective: High-normal albuminuria has recently been associated with an elevated risk of cardiovascular disease. However, it is uncertain whether high-normal albuminuria is associated with metabolic syndrome (MetS). The objective of this prospective cohort study was to investigate whether a temporal relationship exists between a high-normal urine albumin-to-creatinine ratio (UACR) and the development of MetS.
Study design: A total of 4338 healthy Korean men who had their UACRs and MetS components assessed in 2005 were enrolled in the study. A MetS-free cohort of 1364 individuals, who did not have any conditions that would have excluded them from the study, was followed up until 2010.
Main outcome measure: MetS was defined according to the joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention.
Results: Cox proportional hazards models were used to estimate the hazard ratio (HR) associated with normal UACR values stratified into following tertiles: <3.12 μg/mg, ≥3.12, <4.87 μg/mg, and ≥4.87 μg/mg. The UACR was categorised into the following tertiles. During 4470.6 person-years of follow-up, 247 incident cases of MetS developed between 2006 and 2010. The third UACR tertile was associated with the development of MetS after adjusting for multiple baseline covariates (HR 1.57; 95% confidence interval: 1.14–2.18).
Conclusions: On the basis of our 5-year follow-up study, a high-normal UACR predicts the development of MetS in Korean men.

1. Introduction

Microalbuminuria has traditionally been a prognostic marker for the detection of chronic kidney disease [1]. Many studies suggest that microalbuminuria is strongly associated with an increased risk of cardiovascular disease [2], and people who have metabolic syndrome (MetS) are at an increased risk of developing cardiovascular disease, diabetes, and all-cause mortality [3]. Several cross-sectional studies in different countries [4,5] have reported a close relationship between microalbuminuria and MetS. Further, the PREVEND study showed that elevated excretion of albumin in the urine should be added to the as one of the MetS components, which was defined by the International Diabetes Federation to more reliably predict the development of type 2 diabetes mellitus (T2DM), chronic kidney disease, and cardiovascular disease [6].

High albuminuria, even within normal range levels, has recently found to be associated with elevated risks of cardiovascular diseases and deaths according to the Strong Heart Study [7] and BENEDICT trial [8]. In addition, hypertension and T2DM have also been associated with a high albuminuria level within the normal range [9,10]. These studies suggest that components of MetS, which are risk factors for cardiovascular disease, are also associated with high-normal albuminuria levels. Low-grade albuminuria within the normal range is often observed within the normal population [11]. The culmination of recent evidence appears to be threatening the 'classic' definition of microalbuminuria.

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A cross-sectional study in Greece demonstrated that increasing levels of albumin excretion are associated with an increasing prevalence of MetS with hypertension [12]. However, there was no significant association between urine albumin-to-creatinine ratio (UACR) within the normal range and MetS after adjusting for multiple covariates. Until now, it has been unclear whether high albuminuria within the normal range is associated with MetS. In addition, these studies are cross-sectional studies.

To the best of our knowledge, no prospective cohort studies have investigated on the relationship between albuminuria within the normal range (<30 μg/mg) and the development of MetS. Therefore, we conducted a prospective cohort study to examine the temporal relationship between a UACR within the normal range and the development of MetS among Korean men.

2. Materials and methods

2.1. Study design

A prospective cohort study was undertaken to examine the temporal relationship between UACR in the normal range and the development of MetS in Korean men who participated in a medical check-up programme at the Health Promotion Centre at the Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, Korea. The study procedures have been detailed previously [13]. The purpose of the medical check-up programme is to promote employee health and to improve the early detection of existing diseases. All employees participate in either annual or biennial health check-ups, as required by Korea's Industrial Safety and Health Law. The study population was mostly comprised of company employees and their family members from across Korea.

2.2. Study population

A total of 4338 men, who attended a medical check-up in 2005 and had been assessed for their UACRs and MetS components, were considered potential participants in this study. Of the 4338 participants, 1523 men were excluded for different reasons as follows: 35 had a past history of malignancy; 73 had a past history of cardiovascular disease; 368 were receiving lipid-lowering medication; 217 had microalbuminuria ($30 \leq$ UACR < 300 μg/mg); 24 had overt albuminuria (UACR ≥ 300 μg/mg); and 1122 were diagnosed as having baseline MetS initial examination. Given that some of the participants had more than one exclusion criterion, the total number of men who were eligible for the study was 2815. We excluded a further 1451 participants who did not attend any follow-up visits between 2006 and 2010. Accordingly, 1364 participants were included in the final analysis and were observed for MetS development (Fig. 1). The total follow-up period was 4470.6 person-years and the mean follow-up period was 3.28 (±1.52) person-years. Ethical approval for the study protocol and analysis of the data was obtained from the Institutional Review Board of Kangbuk Samsung Hospital. Written informed consent was obtained from all participants.

2.3. Clinical and laboratory measurements

Study data included a medical history, a physical examination, information derived from a questionnaire, anthropometric measurements, and laboratory measurements. The medical history and the history of prescription-drug use were assessed by the examining physicians. All the participants were asked to complete a health-related behaviour questionnaire. Questions about alcohol intake included the frequency of alcohol consumption on a weekly basis and the typical amount that was consumed each day (≥20 g/day). We considered persons who reported that they

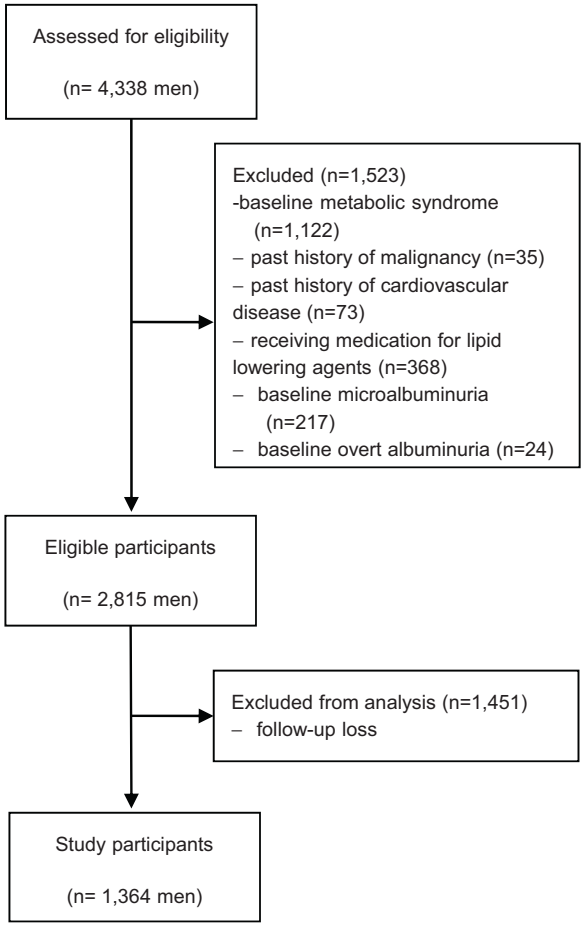

Fig. 1. Flow chart for the selection of study participants.

smoked at the time of the study to be current smokers. In addition, participants were asked about whether they participated in physical activities per week, such as jogging, bicycling, and swimming that lasted long enough to cause perspiration. Regular exercise was defined as physical activity of moderate intensity more than once a week. T2DM was defined as either a fasting serum glucose level of at least 126 mg/dL or the current use of blood-glucose-lowering agents. Hypertension was defined as either current use of antihypertensive medication or having a measured blood pressure (BP) ≥140/90 mmHg during initial examinations. Trained nurses obtained sitting BP levels with a standard mercury sphygmomanometer. The first and fifth Korotkoff sounds were utilised to estimate systolic and diastolic BP.

Blood samples were collected after fasting for >12 h and were drawn from an antecubital vein. Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyl transferase were measured using Bayer Reagent Packs (Bayer HealthCare, Tarrytown, NY) on an automated chemistry analyser (ADVIA 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). High-sensitivity C-reactive protein (hsCRP) level was analysed using particle-enhanced immunonephelometry using the BN™ System (Dade Behring Co., Marburg, Germany). Insulin levels were measured using immunoradiometric assays (Biosource, Nivelles, Belgium). Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) described by Matthews et al. [14]: Fasting serum insulin (μU/dL) × fasting serum glucose (mmol/L)/22.5. Serum creatinine (SCr) levels were measured using the alkaline picrate or Jaffe, method. Kidney function was estimated from the glomerular filtration rate (GFR), which was calculated using the Chronic