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Evaluation of risk for metabolic syndrome according to the fasting insulin concentration in Korean men

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ABSTRACT

Background: As a well-known risk factor for cardiovascular disease, metabolic syndrome (MetS) is an important global health problem due to its high worldwide prevalence. The objective of this study is to determine whether the fasting serum insulin concentration influences future incidence of MetS.
Methods: A total of 14,621 Korean men without MetS participating in a medical health check-up program were followed up from 2005 until 2010. They were divided into 4 groups according to baseline fasting insulin concentrations. The incidence of MetS was compared among the groups, and Cox proportional hazards model was used to determine if MetS was associated with higher fasting insulin concentration.
Results: The incidence of MetS increased according to the baseline fasting insulin concentration (first quartile: 8.4%, second quartile: 12.3%, third quartile: 16.3%, fourth quartile: 26.5%, $P < 0.001$). Even after adjusting for multiple covariates, the hazard ratio (95% CI) for MetS was higher for the second (1.13 (0.93–1.37)), third (1.29 (1.06–1.56)) and fourth quartile group (1.70 (1.36–2.13)), compared to the first quartile group (P for trend <0.001).
Conclusion: The incidence of MetS increased proportionally to fasting insulin concentration. Additionally, increased fasting insulin concentration was an independent risk factor for the future development of MetS.

1. Introduction

Metabolic syndrome (MetS) is characterized by a cluster of increased glucose concentration, overweight, dyslipidemia, hypertension, central obesity, and is a risk factor of type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) [1–7], stroke [8,9], malignancy [10] and many other diseases. The prevalence of MetS is increasing in U.S. and many other countries, even though it has already been common disease [1–4,11–13]. Over past few decades, sedentary lifestyle and overweight have become common in many countries, with accompanying MetS becoming a global health problem. The prevalence and complications of MetS including CVD and T2DM will likely continue [1,3,7,11–13].

Because of this clinical importance, there have been many studies about diagnosis, treatment, epidemiology, and pathophysiology of MetS. So far, studies on the diagnosis of MetS have focused on diagnostic criteria [3,7]. Although early diagnosis and prediction of MetS is a clinically interesting topic, relatively few studies have addressed this topic. Two previous studies reported that increased fasting insulin concentration predicts the future incidence of MetS in the general population [14,15].

On the other hand, insulin resistance is believed to play an importance role in pathogenesis of MetS [3,7,16,17]. Hyperinsulinemia is an early clinical manifestation of insulin resistance [18]. Fasting insulin concentration could rise prior to the occurrence of overt MetS, and increased fasting insulin concentration may predict future incidence of MetS. However, to the best of our knowledge, limited data supports this hypothesis.

2. Materials and methods

2.1. Study design

A prospective cohort study was conducted to examine the association between fasting serum insulin concentrations and the development of MetS in Korean men participating in a medical health check-up program at the health promotion center of Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, Korea. The study methods

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have been described in detail previously [19]. The purpose of the medical health check-up program is to promote the health of the employees and to enhance early detection of existing diseases. All employees participate in either annual or biennial health check-up, as is required by Korea's Industrial Safety and Health law. Most of the costs of the medical examinations are typically paid by their employers. This study population was mainly employees and family members of various industrial companies nationwide.

2.2. Study population

A total of 28,417 men who had been examined for MetS components during a medical check-up in 2005 participated. Among them, 7710 men were excluded based on the following exclusion criteria that might influence MetS or fasting serum insulin: 149 had a past history of a malignancy; 225 had a past history of cardiovascular disease; 2104 were receiving medication for lipid-lowering agents; 1638 had a baseline diabetes mellitus and 5345 were diagnosed as baseline MetS at initial examinations. Because some participants had more than one exclusion criteria, the total number of men who were eligible for the study was 20,707. We further excluded 6086 participants who did not attend any follow-up visit between 2006 and 2010. Without the follow-up visit, we could not identify the development of MetS and could not also calculate the individual person year. Accordingly, 14,621 participants were included in the final analysis and were observed for the development of MetS. Ethical approval for the study protocol and analysis of the data were obtained from the institutional review board of Kangbuk Samsung Hospital. The informed consent requirement was exempted by the Institutional Review Board because researchers only accessed retrospectively a de-identified database for analysis purposes. Our study performed in accordance with the 1975, as revised in 2008 ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration

2.3. Clinical and laboratory measurements

Study data included a medical history, physical examination, information provided by a questionnaire, anthropometric measurements and laboratory measurements. The medical history and the history of drug prescription were assessed by the examining physicians. All participants were asked to respond to a questionnaire on health-related behavior. Questions about alcohol intake included the frequency of alcohol consumption on a weekly basis and the usual amount consumed on a daily basis (≥20 g/day). We considered persons reporting that they smoked at that time to be current smokers. In addition, the participants were asked about their weekly frequency of physical activity, such as jogging, bicycling, and swimming that lasted long enough to produce perspiration (≥1 time/week). Diabetes mellitus was defined as fasting serum glucose of at least 126 mg/dl or current use of blood glucose-lowering agents at initial examinations. Hypertension was defined as either the current use of antihypertensive medication or as having a measured blood pressure (BP) ≥140/90 mmHg at initial examinations. Trained nurses obtained sitting BP concentrations using a standard mercury sphygmomanometer. The first and fifth Korotkoff sounds were utilized in order to estimate the systolic and diastolic BP.

Blood samples were collected after >12 h of fasting and were drawn from an antecubital vein. Serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltransferase (GGT) were measured using the ADVIA 1650 chemistry analyzer (Bayer Diagnostics). High-sensitivity C-reactive protein (hsCRP) was analyzed by the BN™ System (Dade Behring). Insulin concentrations were measured with immunoradiometric assays (Biosource). Insulin resistance was calculated with the homeostasis model assessment of insulin resistance (HOMA-IR) as described by Matthews et al. [20] as fasting serum insulin (μU/dl) × fasting serum glucose (mmol/l)/22.5. Kidney function was measured with estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [21].

The fasting serum glucose was measured with the hexokinase method. Total cholesterol and triglyceride were measured with enzymatic colorimetric tests, low-density lipoprotein (LDL) cholesterol was measured with the homogeneous enzymatic colorimetric test, and high-density lipoprotein (HDL) cholesterol was measured with the selective inhibition method (Bayer). Height and weight were measured after an overnight fast with the shoeless participants wearing a lightweight hospital gown. Waist circumference (WC) was measured in the standing position, at the concentration of umbilicus by a single examiner. The clinical laboratory has been accredited and participates annually in inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories. The diagnosis of fatty liver was based on the results of abdominal ultrasonography (US) with a 3.5-MHz transducer (Logic Q700 MR, GE). Abdominal US were carried out by experienced radiologists who were unaware of the aims of the study and blind to the laboratory values. Images were captured in a standard fashion, with the patient in the supine position, with the right arm raised above the head. The fatty liver was diagnosed according to the standard criteria described by previous studies, including parenchymal brightness, liver-to-kidney contrast, deep beam attenuation, and bright vessel walls [22–24].

The presence of MetS was made according to the joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention [4]. Increased BP was defined as a systolic or diastolic BP ≥ 130/85 mmHg; increased fasting serum glucose concentration was defined as ≥100 mg/dl; high serum triglyceride concentrations were defined as ≥150 mg/dl; low HDL-cholesterol concentrations were defined as <40 mg/dl in men and increased WC was defined as >90 cm in men. MetS was defined as the presence of three or more of the above components.

2.4. Statistical methods

Data were expressed as means ± SD or medians (interquartile range) for continuous variables and percentages of the number for categorical variables. The one-way ANOVA and χ^2-test were used to analyze the statistical differences among the characteristics of the study participants at the time of enrollment in relation to the quartile groups of fasting serum insulin concentrations. The distributions of continuous variables were evaluated, and log transformations were used in the analysis as required. Because we could not know the exact time for incident MetS, the time of MetS development was assumed to be the midpoint between the visit at which MetS was first diagnosed and the baseline visit (2005). The person years were calculated as the sum of follow-up times from the baseline until an assumed time of MetS development or until the final examination of each individual. To evaluate the associations of baseline fasting serum insulin concentrations and incident MetS, we used Cox proportional hazards models to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for incident MetS comparing the highest three quartiles of baseline fasting serum insulin *vs* the lowest quartile. Cox-proportional hazard models were adjusted for the multiple confounding factors. In the multivariate models, we included variables that might confound the relationship between fasting serum insulin and MetS, which include age, total cholesterol, log(hsCRP), HOMA-IR, eGFR, GGT, number of baseline MetS component, recent smoking status, regular exercise and alcohol intake and hypertension. For the linear trends of risk, the number of quartiles was used as a continuous variable and tested on each model. To use the Cox proportional hazards models, we checked the validity of the proportional hazards assumption. Two approaches were used to assess the validity of the proportional hazards assumption. First, the assumption was assessed by log-minus-log survival function and found to graphically hold. Second, to confirm the validity of the proportional