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Additive effect of non-alcoholic fatty liver disease on the development of diabetes in individuals with metabolic syndrome

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) is considered as the hepatic manifestation of the metabolic syndrome (MetS), with insulin resistance as the common pathophysiology. In a current longitudinal cohort study, we evaluated the separate and combined effects of MetS and NAFLD on incident diabetes risk.

Methods: Participants were categorized into four groups on the basis of the presence of NAFLD and MetS at baseline (i.e., with NAFLD, with MetS, with both, or without either). We compared the development of diabetes among these four groups.

Results: During the mean follow up of 4 years, 435 of the 7849 participants (5.5%) developed diabetes. The age, sex, and smoking-adjusted risk of incident diabetes was higher in the NAFLD only group (HR 1.51, 95% CI 1.14–1.99), MetS only group (HR 2.82, 95% CI 2.01–3.95), and both group (HR 5.45, 95% CI 4.32–6.82) compared with the group of neither. When compared with the NAFLD only group, the adjusted HR for incident diabetes was 1.87 (95% CI 1.29–2.72) in the MetS only group and 3.62 (95% CI 2.74–4.77) in both group. Among individuals with MetS, the presence of NAFLD showed a significant increase in risk of incident diabetes even after further adjustment for MetS components including fasting glucose, TG, BMI, systolic BP, and HDL-C (HR 1.53, 95% CI 1.09–2.16).

Conclusion: The presence of NAFLD further increased the risk of incident diabetes in individuals with metabolic syndrome. Our results suggest that the coexistence of NAFLD has an additive effect on the development of diabetes in individuals with MetS.

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1. Introduction

Metabolic syndrome (MetS) is a clustering of several atherogenic metabolic abnormalities that include central obesity, impaired glucose metabolism, dyslipidemia, and hypertension [1]. Insulin resistance is considered to play a fundamental role in MetS and leads to the most of the abnormalities observed in MetS [2,3]. Non-alcoholic fatty liver disease (NAFLD) is characterized by lipid deposition in hepatocytes and includes wide spectrum of liver damage from simple steatosis to steatohepatitis and advanced fibrosis [4]. Currently, NAFLD is considered as the hepatic manifestation of MetS, with insulin resistance as the main pathogenic mechanism [5,6]. Insulin resistance is a major factor in the pathogenesis of type 2 diabetes and is closely linked to cardiovascular disease [3,7]. Diagnosing and treating MetS is important since individuals with MetS are at increased risk of developing type 2 diabetes and cardiovascular disease [1,8]. Several studies have reported that NAFLD contribute to the development of type 2 diabetes and is associated with increased cardiovascular risk [9–12].

MetS and NAFLD share a common pathophysiologic mechanism [2,5]. Many individuals with MetS also have NAFLD [13]. Thus, the coexistence of NAFLD may have effect on the contribution of MetS to the development of diabetes. However, the additive role of NAFLD on the incident diabetes risk in individuals with MetS is uncertain. Also, accumulating evidence suggests that the association of NAFLD with insulin resistance is independent of obesity and other metabolic components [6]. However, the magnitude of diabetes risk in NAFLD patients without MetS or in MetS patients without NAFLD is unclear, given the paucity of data on the separate effects of MetS and NAFLD on the development of diabetes [14].

It is important to understand the role of metabolic syndrome and NAFLD on the development of diabetes. The current longitudinal cohort study evaluated the separate and combined effects of metabolic syndrome and NAFLD on incident diabetes risk.

2. Patients and methods

We used the same data sources and methods as our previous study [9]. These are described below, along with additional methodological details.

2.1. *Study population*

More than 90,000 people undergo a comprehensive health check-up each year at Kangbuk Samsung Hospital Total Healthcare Center. The employees of various industrial companies and their spouses account for a considerable proportion of the examinees. The purpose of these medical health checkup programs is to promote the health of employees through regular health checkups and to enhance early detection of existing diseases. The costs of examinations are largely paid for by the companies to promote the health of the employees and their family members. A considerable proportion of examinees undergo examinations annually or biennially.

Initial data were obtained from 10,950 subjects who participated in comprehensive health check-ups annually for 5 years (between January 2005 and December 2009). Among these subjects, 3101 were excluded for the following reasons based on the 2005 record: (1) alcohol intake >20 g/day ($n = 1755$); (2) self-reported diabetes or undiagnosed diabetes (fasting glucose concentration ≥126 mg/dL or hemoglobin A1c (HbA1c) ≥ 6.5%; $n = 437$); (3) positive serologic markers for hepatitis B ($n = 558$) or C ($n = 17$) virus; (4) liver cirrhosis ($n = 8$); and (5) absence of data including ultrasonographic data ($n = 728$). All analyses were performed on the remaining 7849 subjects (5409 males and 2440 females, ≥20 years of age; mean age, 44.5 years).

This study was approved by the Institutional Review Board at Kangbuk Samsung Hospital. Informed consent requirement for this study was waived by the Institutional Review Board because the researcher accessed the database for analysis purposes only and personal information was not retrieved.

2.2. *Study design and statistical analysis*

This was a retrospective longitudinal cohort study. Participants were categorized into four groups on the basis of the presence of NAFLD and MetS at baseline as follows: (1) no NAFLD or MetS; (2) NAFLD without MetS; (3) MetS without NAFLD; and (4) both NAFLD and MS. The one way ANOVA and Pearson's chi-square test were used to analyze differences in the baseline characteristics between four study groups. Results are expressed as the number of subjects, with percentages in parentheses, or as the mean ± standard deviation. We compared the development of diabetes between the study groups during the follow-up period using the hazard ratios (HRs) and cumulative hazard plots for incident diabetes, as estimated by Cox's proportional hazard analysis. The time scale for the analysis was the time since the basal examination until development of diabetes, or the last follow-up visit. Data were analyzed using SPSS version 22 (IBM SPSS Inc., Chicago, IL, USA). P value less than 0.05 was considered statistically significant.

2.3. *Measurements*

Heights and body weights were measured while the subjects were barefoot and wearing light clothing. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Blood pressure (BP) was measured using a standardized sphygmomanometer after 5 min of rest. Blood samples were collected from the antecubital vein after an overnight fast. Fasting blood glucose, triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) were measured using