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Impact of hyperinsulinemia on the development of hypertension in normotensive, nondiabetic adults: a 4-year follow-up study

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ABSTRACT

Background and Aims. This study aimed to investigate the association between baseline fasting insulin levels, changes in fasting insulin levels, and future development of hypertension in normotensive, non-diabetic, healthy adults.

Methods. We analyzed data from 11,123 adults, aged 20–65 years, who had no history of hypertension or diabetes mellitus at a 2004 medical examination in a health promotion program and had attended a repeat examination in 2008. Subjects were divided into four groups according to baseline quartiles of fasting insulin and dichotomized fasting insulin levels at baseline and after 4 years: low–low, low–high, high–low, high–high. We also assessed whether the association differed between the younger (20–40 years) and older subjects (41–65 years).

Results. In four years, 1142 subjects (10.3%) developed hypertension. The odds ratio (OR) for the development for hypertension increased as the quartiles of baseline fasting insulin levels and changes in fasting insulin levels increased from the first to the fourth quartile (OR 1.15, 1.35, and 1.95 vs. 1.07, 1.22, and 1.41, respectively), after adjusting for multiple factors. The OR for hypertension was 2.0-fold higher in the high–high group and 1.34-fold higher in the low–high group than in the low–low group. In comparing the results by age group, we found that these relationships were more prominent in younger subjects.

Conclusion. High baseline and continuously increasing fasting insulin levels appeared to be independent determinants for the future development of hypertension during this 4-year follow-up study in normotensive, non-diabetic, healthy adults.

1. Introduction

Previous studies have identified multiple molecular and cellular mechanisms through which elevated insulin levels or insulin resistance increase blood pressure [1–4]. Insulin resistance, hyperinsulinemia, and blood pressure have been correlated not only in the obese, but also in lean hypertensive subjects [5,6]. The mechanism through which hyperinsulinemia or insulin resistance is associated with hypertension and blood pressure is not fully known. Insulin was shown to

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; OR, odds ratio; CI, confidence interval.

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simulate the sympathetic nervous system, increase renal sodium retention, modulate cation transport, and induce vascular smooth muscle hypertrophy [7,8]. Hyperinsulinemia also might impair endothelium-dependent vasodilation in large conduit arteries by increased oxidative stress [9]. It is plausible that insulin resistance through the concomitant compensatory hyperinsulinemia could contribute the pathogenesis of hypertension by one or more of these mechanisms. Some experimental studies also suggest that rodents with genetic or diet-induced hypertension showed hyperinsulinemia and insulin resistance, and blood pressure was decreased by improving insulin sensitivity [10–12].

Despite its health significance, the respective contribution of elevated insulin levels or insulin resistance to the likelihood of developing hypertension is poorly defined. Although several studies have been published, the cause-and-effect relationships between hypertension and hyperinsulinemia cannot be confirmed due to the cross-sectional nature of the studies, scarcity of longitudinal studies, small numbers of study participants, and the inability to demonstrate independence using established risk factors for hypertension [13–15].

Thus, the aim of this longitudinal study was to quantify the respective contributions of baseline fasting insulin levels and changes in fasting insulin levels to the development of hypertension in normotensive and nondiabetic adults. We performed this study to determine how changes in insulin levels could affect hypertension development in healthy Korean adults during a 4-year follow-up period. We also separately investigated this association after stratifying the subjects into two groups based on age: younger (20–40 years) and older (41–65 years).

2. Materials and methods

2.1. Study population

We analyzed data from 29,642 participants in a medical health checkup program at the Health Promotion Center of Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, Korea. In 2004, subjects aged 20–65 years participated in the medical checkup program. We excluded subjects who were hypertensive at baseline (defined as systolic blood pressure [SBP] ≥140 mmHg, diastolic blood pressure [DBP] ≥90 mmHg, or self-reported history of antihypertensive drug use in the past 2 weeks), had a fasting blood glucose (FBG) level ≥7.0 mmol/l or currently used blood glucose-lowering medication, had a history of malignancy, cardiovascular disease, cerebrovascular disease, known liver disease, abnormal thyroid function, or who had missing data relevant to the analyses. A total of 20,707 subjects were eligible for the study at baseline, 11,123 of whom were reexamined after 4 years. Physical activity, alcohol intake, and smoking status were assessed by self-administered questionnaires. Questions about alcohol use assessed the frequency of alcohol consumption on a weekly basis and current alcohol use was dichotomized as 'yes' or 'no.' We defined subjects who reported that they smoked as 'current smokers.' Regular exercise was assessed using a physician-administered questionnaire in which subjects were asked if they participated in regular exercise 'at least once a week' or 'never.' Ethics approval for the study protocol and analysis of the data was obtained from the Institutional Review Board of Kangbuk Samsung Hospital.

2.2. Anthropometric and BP measurements

All anthropometric and BP measurements were carried out according to standard protocols. Study participants were asked to wear light indoor clothing during the measurements. Weight was measured to the nearest 0.1 kg using a digital weight scale. Height was measured to the nearest 0.1 cm. Body mass index (BMI) was calculated by dividing weight (kg) by the height (m) squared.

Blood pressures were taken with a standardized mercury manometer between 08:00 AM and 10:00 AM after at least 5 min of rest, according to the Hypertension Detection and Follow-up Program protocol [16]. Trained nurses measured seated BP. When the SBP or DBP exceeded 140 mmHg or 90 mmHg, it was remeasured after a 5 min rest, and the results averaged. Height, weight, SBP and DBP were measured in duplicate, and the results were averaged. Hypertension was defined as SBP≥140 mmHg, DBP ≥90 mmHg, or a history of hypertension during 2004–2008.

2.3. Laboratory methods

After 12 h of fasting, blood samples were collected and checked for fasting blood glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels. The hexokinase method (Advia 1650 Autoanalyzer, Bayer Diagnostics, Leverkusen, Germany) was used to measure blood glucose levels, and an enzymatic colorimetric test was used to measure total cholesterol and triglyceride levels. The selective inhibition method was used to measure levels of HDL-C and a homogeneous enzymatic calorimetric test was used to measure levels of LDL-C. Serum insulin concentrations were measured with an immunoradiometric assay (INS-Irma, 5 Biosource, Belgium), with intra- and inter-assay coefficients of variation of 1.6%–2.2% and 6.1%–6.5%, respectively. The homeostasis model assessment of insulin resistance (HOMA-IR), was assessed according to the following equation: fasting blood insulin (μU/ml) × fasting blood glucose (mmol/l)/22.5 [17].

2.4. Statistical analysis

The relationships between baseline insulin level and future development of hypertension were analyzed in three steps. First, the risk for future development of hypertension was analyzed according to groups stratified by baseline fasting insulin levels. Subjects were grouped into quartiles according to baseline insulin levels (pmol/l) to simplify the interpretation of the results of subsequent analyses: Groups I (≤50.07), II (50.14–60.42), III (60.56–72.99), and IV (≥ 73.27). We estimated the adjusted odds ratio (OR) and 95% confidence interval (CI) for hypertension using multiple logistic regression analyses after adjustment for age, sex, BMI, percent weight change, smoking status, alcohol consumption, regular exercise, SBP, fasting glucose, triglyceride, and HDL-C levels at baseline.