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

Se Eun Park^{a,b}, Eun-Jung Rhee^a, Cheol-Young Park^a, Ki Won Oh^a, Sung-Woo Park^a, Sun-Woo Kim^a, Won-Young Lee^{a,*}

^a Department of Endocrinology and Metabolism, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

^b Department of Medicine, the Graduate School of Yonsei University, Seoul, Korea

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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.

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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.

* *Corresponding author.* Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk, Samsung Hospital, Sungkyunkwan University School of Medicine, no. 108 Pyung-Dong, Jongro-Ku, Seoul 110-746, South Korea.

E-mail address: drlwy@hanmail.net (W.-Y. Lee).

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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 ($\mu\text{U/ml}$) \times 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.

Second, to analyze the effect of variability in insulin level during the 4-year study interval on the development of hypertension, subjects were divided into four groups according to dichotomized fasting insulin level at baseline and after 4 years: low–low, low at baseline and after 4 years; low–high, low at baseline and high after 4 years; high–low, high at baseline and low after 4 years; high–high, high at baseline and still high after 4 years. A low grade means that an insulin level was within the lower half of the range and a high grade means that an insulin level was within the higher half of the range. After adjustment for age, sex, BMI, percent weight change, smoking status, alcohol consumption, regular exercise, SBP, fasting glucose, triglyceride, HDL-C, and insulin levels at baseline, logistic regression analysis was performed to determine ORs for the development of hypertension according to the four dichotomized fasting insulin level groups during the 4-year study period.

Third, ORs for hypertension according to changes in insulin level after adjustment for confounding factors during the 4-year follow-up were analyzed using logistic regression analysis. Changes in insulin level were calculated by subtracting the 2004 fasting insulin level from the 2008 level. The subjects were divided into four groups according to changes in insulin levels (pmol/l): Groups I (≤ -27.09), II (-27.02 to -10.27), III (-10.28 to 7.01), and IV (≥ 7.08).

Finally, to observe the effects of age on the relationship between hyperinsulinemia and the development of hypertension, we also assessed whether the association differed between the younger (20–40 years) and older subjects (41–65 years). We used Student's *t*-test or the Mann–Whitney test for comparison of continuous variables and the χ^2 test for comparison of categorical variables. Bivariate correlation analyses between changes in insulin levels for 4 years and

the metabolic parameters were performed using Pearson's correlation analysis. Analyses were performed using SPSS for Windows software (version 17.0; SPSS, Chicago, IL). All reported *P*-values < 0.05 were considered statistically significant.

3. Results

The baseline characteristics of the study population according to the development of hypertension are shown in Table 1. The mean (\pm SD) age was 39.4 (\pm 6.43) years and 65.6% of the participants were male. The mean BMI was 23.6 ± 2.9 kg/m², and the prevalence of overweight (BMI ≥ 23 kg/m²) and obese (BMI ≥ 25 kg/m²) individuals was 26.2% and 30.9%, respectively. The mean values of SBP and DBP were 114.9 ± 12.3 mmHg and 74.4 ± 9.2 mmHg, respectively. Subjects with hypertension at year 4 were older and more likely to be male and obese. Furthermore, subjects with hypertension had a greater number of adverse risk factors than those without hypertension, including higher baseline levels of SBP, DBP, fasting glucose, total cholesterol, triglyceride, LDL-C, and plasma insulin, and lower HDL-C levels. This group was also more likely to smoke, consume more alcohol, and exercise less.

After four years, 1142 subjects (10.3%) developed hypertension and 842 subjects (7.3%) developed diabetes. Changes in insulin levels over 4 years were significantly associated with percent weight change ($r=0.103$, $P < 0.001$), changes in fasting glucose ($r=0.171$, $P < 0.001$), and triglyceride ($r=0.148$, $P < 0.001$) levels. When the ORs for the development of hypertension according to baseline fasting insulin level quartile were analyzed with logistic regression analyses adjusting for confounding factors, subjects in the highest baseline fasting insulin level quartile had the highest OR for

Table 1 – Baseline characteristics of participants by hypertension status at 4 years.

Characteristics	Total	Hypertension	No hypertension	<i>P</i>
N	11,123	1142	9981	
Age, years	39.4 \pm 6.4	41.4 \pm 6.8	39.2 \pm 6.3	<0.001
Male, %	65.6	84.8	63.4	<0.001
Body mass index, kg/m ²	23.6 \pm 2.9	25.5 \pm 2.9	23.4 \pm 2.8	<0.001
Smoking, %				<0.001
No	54.8	43.3	56.1	
Ex	17.7	24.2	17.0	
Current	27.5	32.5	26.9	
Current alcohol use, %	53.4	52.1	33.5	<0.001
Regular exercise, %				<0.001
Never	49.0	41.4	49.9	
≥ 1 /week	51.0	58.6	50.1	
SBP, mmHg ^a	114.9 [114.7, 115.2]	127.6 [126.9, 128.4]	113.4 [113.3, 113.7]	<0.001
DBP, mmHg ^a	74.4 [74.2, 74.6]	83.8 [84.9, 82.9]	73.4 [73.2, 73.6]	<0.001
Fasting glucose, mmol/l	5.20 \pm 0.66	5.37 \pm 0.81	5.19 \pm 0.64	<0.001
Total cholesterol, mmol/l	4.94 \pm 0.85	5.18 \pm 0.83	4.91 \pm 0.85	<0.001
Triglyceride, mmol/l	1.23 [0.86, 1.77]	1.53 [1.11, 2.15]	1.19 [0.85, 1.73]	<0.001
HDL-cholesterol, mmol/l	1.48 \pm 0.30	1.44 \pm 0.28	1.48 \pm 0.30	<0.001
LDL-cholesterol, mmol/l	2.98 \pm 0.74	3.18 \pm 0.73	2.96 \pm 0.74	<0.001
Insulin, pmol/l	60.5 [50.1, 73.4]	65.0 [53.3, 81.7]	60.1 [49.9, 72.6]	<0.001
HOMA-IR	1.71 [1.17, 2.28]	2.06 [1.50, 2.79]	1.67 [1.13, 2.23]	<0.001

Data were summarized as mean \pm standard deviation or median [25th percentile, 75th percentile] unless specified otherwise.

^a Systolic and diastolic blood pressures were expressed as mean [95% confidence interval].

Table 2 – Odds ratios for the development of hypertension over 4 years according to quartile groups of baseline fasting insulin levels.

Quartiles of baseline fasting insulin levels (pmol/l)	n	Incident cases, n (%)	Odds ratio	95% CI	P
I (≤50.07)	2780	215 (7.7)	1.00	-	-
II (50.14–60.42)	2787	234 (8.4)	1.15	0.95, 1.41	0.16
III (60.56–72.99)	2732	268 (9.8)	1.35	1.11, 1.64	0.003
IV (≥ 73.27)	2824	395 (14.1)	1.95	1.61, 2.35	<0.001

Adjusted for age, sex, BMI, percent weight change, smoking status, alcohol consumption, regular exercise, systolic blood pressure, fasting glucose, triglyceride, and HDL-C levels at baseline.

the development of hypertension among the quartile groups (OR 1.95; 95% CI, 1.61–2.35) (Table 2).

When ORs were compared in the four groups that were divided by dichotomized insulin status at baseline and 4 years later, the high–high group showed a 2.00-fold increased risk of hypertension over the low–low group (95% CI 1.69–2.38). Similarly, the low–high group showed a 1.34-fold increased risk of hypertension over the low–low group. However, the high–low group did not have a significantly increased risk of hypertension compared to the low–low group (OR 1.22, 95% CI 0.99–1.50) (Table 3). The adjusted OR for hypertension was found to be 1.41 (95% CI 1.18–1.70) when comparing the highest and lowest quartiles of changes in fasting insulin level. The risk of developing hypertension also increased from the first to the fourth quartile of changes in fasting insulin level, after adjustment for confounding variables (Table 4).

During 4 years of follow-up period, the groups with older subjects showed a higher incidence for hypertension compared with the groups with younger subjects (14.0 % vs. 7.6%, $P < 0.001$). As shown graphically in Fig. 1, the impact of baseline hyperinsulinemia, changes in insulin levels, and insulin grades at baseline and after 4 years on the development of hypertension seemed stronger for younger subjects than for older subjects (Supplementary table 1–3). There were no significant associations between age and hyperinsulinemia in the older subjects ($P = 0.709$ for baseline hyperinsulinemia, $P = 0.530$ for changes of insulin levels, and $P = 0.955$ for insulin grades at baseline and after 4 years).

4. Discussion

Hypertension is a remarkably common condition and frequently leads to cardiovascular sequelae, including stroke and myocardial infarction [18]. In this observational cohort

without intentional intervention, subjects with high baseline insulin levels were associated with new-onset hypertension after 4 years of follow-up. Regarding the changes in insulin level during the follow-up period, the risk of hypertension increased from the first to the fourth quartiles. Furthermore, subjects who had a high fasting insulin level at baseline and who still had a high insulin level after 4 years had a significantly higher risk of developing hypertension than subjects who were in the low insulin group at baseline and remained in that group after 4 years.

Despite the fact that hyperinsulinemia itself is considered a major contributor to hypertension [3–6], there is ongoing debate about the relationship between insulin level and BP. Several population-based studies have not detected an association between insulin level and BP, but these studies were limited to samples that included predominantly older individuals or subjects with diabetes, or both [19–23]. Additionally, most published studies are cross-sectional in nature. An elevated insulin level was found to be associated with higher BP in previous studies [24,25]. Others reported that only insulin resistance, not fasting insulin levels, was associated with hypertension, but the relation between insulinemia and/or insulin resistance and hypertension varies among ethnic groups [26,27]. Recently, a study of 1944 normotensive Chinese adults followed for an average of 6.4 years showed that metabolic syndrome predicted incident hypertension; however, that study did not evaluate the relationship between insulin levels and hypertension [15]. Our study showed that the presence of hyperinsulinemia at baseline predicted an increased risk for the future development of hypertension in normotensive and nondiabetic adults.

We also found that subjects with sustained hyperinsulinemia after 4 years of follow-up was associated with a greater risk of developing hypertension compared to those with sustained low insulin levels. The subjects with high insulin

Table 3 – Odds ratios for the development of hypertension over 4 years according to insulin grades at baseline and after 4 years.

Insulin grades in 2004 and 2008	n	Incident case, n (%)	Odds ratio	95% CI	P
Low and low	3463	241 (7.0)	1.00	-	-
High and low	2134	173 (8.1)	1.22	0.99, 1.50	0.062
Low and high	2104	212 (10.1)	1.34	1.10, 1.63	0.004
High and High	3422	497 (14.5)	2.00	1.69, 2.38	<0.001

Adjusted for age, sex, BMI, percent weight change, smoking status, alcohol consumption, regular exercise, systolic blood pressure, fasting glucose, triglyceride, HDL-C, and insulin levels at baseline.

Table 4 – Odds ratios for the development of hypertension over 4 years according to quartiles of insulin level change over 4 years of follow-up.

Quartiles of changes in insulin levels (pmol/l)	n	Incident case, n (%)	Odds ratio	95% CI	P
I (≤ -27.09)	2796	230 (8.2)	1.00	-	-
II ($-27.02 \sim -10.27$)	2780	250 (9.0)	1.07	0.88, 1.29	0.51
III ($-10.28 \sim 7.01$)	2794	301 (10.8)	1.22	1.01, 1.47	0.04
IV (≥ 7.08)	2753	341 (12.4)	1.41	1.18, 1.70	<0.001

Adjusted for age, sex, BMI, percent weight change, smoking status, alcohol consumption, regular exercise, systolic blood pressure, fasting glucose, triglyceride, and HDL-C levels at baseline.

levels after 4 years showed a higher risk of hypertension than subjects with sustained low insulin levels, regardless of baseline insulin level. In contrast, subjects with a high baseline insulin level and a decreased insulin level after 4 years showed a risk of hypertension similar to that of subjects with sustained low insulin levels. Comparing the groups with high insulin level at baseline, changes in insulin level during 4 years were significantly different. Insulin levels were more reduced in high–low group than high–high group (-35.70 [$-46.34 \sim -25.84$] vs. -5.14 [$-16.67 \sim 8.96$] for high–low group vs. high–high group, $P < 0.001$). Hyperinsulinemia accompanied by increased insulin secretion leads to an increase in cardiac output and triglyceride and cholesterol levels [28,29]. Most of these changes have also been associated with increases in BP. Our data also showed that changes in

insulin levels were associated with increase in triglyceride levels over 4 years. These results show the deleterious influence of sustained hyperinsulinemia that subsequently might lead to clinical hypertension.

In subjects with hyperinsulinemia at baseline, the development of hypertension was reduced if the insulin level was not elevated during the follow-up period. This observation was supported by the subsequent analysis that showed that changes in insulin level during that period were positively correlated with risk of developing hypertension. Previous studies have shown that weight loss is one of the most proven interventions for the management of hyperinsulinemia and hypertension [30,31]. However, it appears that the relationship between hyperinsulinemia and the development of hypertension was sustained, independent of the weight change during

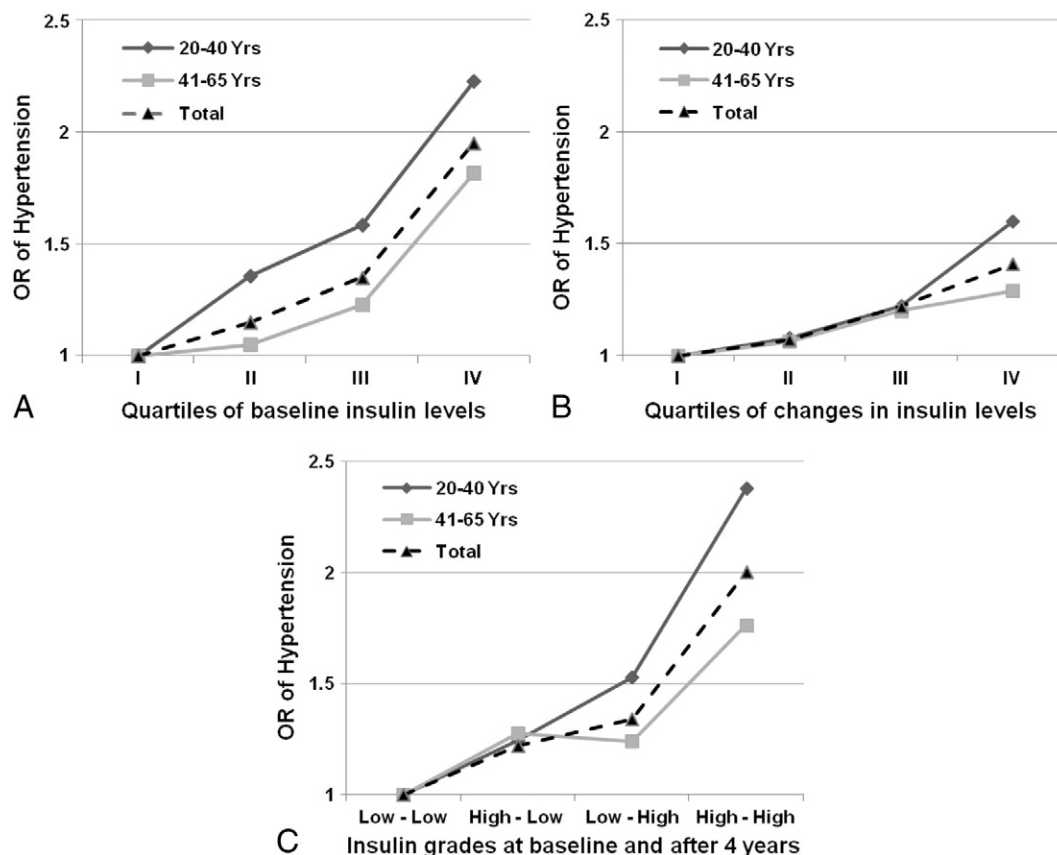


Fig. 1 – Adjusted Odds Ratios for Hypertension by Age in 11,123 Adults. Abbreviation: OR, odds ratio. **A.** Odds ratio of hypertension by age and fasting insulin levels at baseline. **B.** Odds ratio of hypertension by age and changes in insulin levels during 4 years. **C.** Odds ratio of abdominal obesity by age and insulin grades at baseline and after 4 years.

4 years in this study. The mechanism remains unclear, but these results suggest that hyperinsulinemia might play a direct role in increasing BP through other mechanisms that do not fully overlap with weight gain. Insulin sensitizers that increase insulin sensitivity and reduce hyperinsulinemia, also have been shown to have a beneficial effect on the treatment of hypertension [32,33]. These results indirectly demonstrate that, if hyperinsulinemia could be corrected with any intervention, then the development of hypertension might be reduced. Our study differs from others in that we expanded on previous findings by investigating and comparing the effect of baseline hyperinsulinemia, sustained hyperinsulinemia, and changes in insulin levels over 4 years on the development of hypertension among normotensive and nondiabetic adults.

Additionally, our study provides valuable data across a wide age range. The association of insulin levels with the development of hypertension seemed stronger for younger adults than for older adults. The prevalence of hypertension increases markedly with age, such that approximately two thirds of those over 60 years of age have hypertension [34]. However, the mechanism of blood-pressure elevation differs in the elderly compared with younger populations. Age-related stiffening of the large arteries is associated with a decreased capacity of the elastic reservoir, which might lead to hypertension with aging [35]. Both aging related vascular change and hyperinsulinemia might contribute to the development of hypertension. Although the precise mechanisms are not fully understood, current evidence suggests that the mechanisms underlying the development of hypertension might differ between younger and older subjects. Hyperinsulinemia might be a more significant risk factor for the development of hypertension in the younger population. Further studies are needed to investigate the underlying mechanism of this relationship with aging and its implications.

There are several limitations to our study. First, the subjects in our study were selected from among participants in a medical health check-up and are not representative of the general population. Therefore, there might be inherent biases, such as selection bias. Second, this is a retrospective review of longitudinally collected data. The measurements and clinical data were not originally intended for research purposes. Third, incident hypertension was defined based only a one-day basal measurement of BP and again at follow-up or by a self-reported medical history of hypertension. Fourth, we used fasting insulin levels as a measure of insulin resistance. The euglycemic clamp method is a more accurate and reproducible method for measuring insulin resistance, but it is too laborious, and has a low level of patient acceptance, which has limited its use. On the other hand, our selection of fasting insulin levels to assess insulin resistance status has a theoretical background, because hyperinsulinemia at basal status reflects insulin resistance, and hyperinsulinemia per se perpetuates insulin resistance by a wide range of mechanisms [36]. Finally, the overall incidence of hypertension in this cohort during the 4-year observation period was relatively low compared to that reported in other studies [37].

Despite its limitations, the results of this study have clinical value. With a relatively large sample and a long follow-up period, this study suggests that the presence of

hyperinsulinemia at baseline may predict an increased risk for hypertension over a 4-year follow-up period. Furthermore, sustained hyperinsulinemia conferred the highest risk of developing hypertension when compared with subjects with sustained low fasting insulin levels, suggesting the deleterious effects of chronic hyperinsulinemia on the development of hypertension. However, the deleterious effects of basal hyperinsulinemia on hypertension development during that period might be reversed if hyperinsulinemia was corrected, suggesting the reversible and preventive role of reducing hyperinsulinemia on the development of hypertension. Another interesting finding of this study was the different impact of hyperinsulinemia on the development of hypertension across the lifespan. Compared with the older population, the effect of hyperinsulinemia on the development of hypertension seemed stronger in the younger population. Further prospective and interventional studies to reduce hyperinsulinemia are warranted to confirm the significance of hyperinsulinemia on the development of hypertension.

Author contribution

SE Park carried out the data analysis and wrote the manuscript. EJ Rhee, CY Park, KW Oh, SW Park contributed with valuable and critical discussion. Lee WY coordinated the study and drafted the manuscript.

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Conflict of interest

None of the authors has personal or financial conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.metabol.2012.09.013>.

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