Apolipoprotein B Levels Predict Future Development of Hypertension Independent of Visceral Adiposity and Insulin Sensitivity

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Background: High plasma apolipoprotein B (apoB) levels have been shown to be associated with hypertension, central obesity, and insulin resistance in cross-sectional research. However, it is unclear whether apoB levels predict future hypertension independent of body composition and insulin sensitivity. Therefore, we prospectively investigated whether plasma apoB concentrations independently predicted the risk of hypertension in a cohort of Japanese Americans.

Methods: A total of 233 normotensive Japanese Americans (77 men, 156 women; mean age, 46.4 ± 11.0 years) were followed over 10 years to monitor them for the development of hypertension. Fasting plasma concentrations of apoB, glucose, and insulin were measured at baseline. Insulin sensitivity was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR). The abdominal visceral and subcutaneous fat areas were measured at baseline using computed tomography. Logistic regression analysis was used to estimate the association between apoB concentrations and the odds of incident hypertension.

Results: The 10-year cumulative incidence of hypertension was 21.5%. The baseline apoB level was found to be positively associated with the odds of incident hypertension over 10 years after adjustment for age, sex, body mass index, systolic blood pressure, abdominal visceral fat area, abdominal subcutaneous fat area, total plasma cholesterol concentration, diabetes status, and HOMA-IR at baseline (odds ratio and 95% confidence interval for a 1-standard deviation increase, 1.89 [1.06 to 3.37]; \( P = 0.030 \)).

Conclusion: Higher apoB concentrations predicted greater risks of future hypertension independent of abdominal visceral fat area and insulin sensitivity in Japanese Americans.

Keywords: Apolipoproteins B; Hypertension; Intra-abdominal fat; Epidemiology; Prospective studies

INTRODUCTION

Hypertension and dyslipidemia are established modifiable risk factors for cardiovascular disease that frequently coexist [1]. Several epidemiological studies have demonstrated a positive association between serum cholesterol levels and blood pressure (BP) [2-4]. Furthermore, hypertension and dyslipidemia are components of metabolic syndrome that may share a common
The study population was selected from participants in a prospective study of Japanese Americans (the Japanese American Community Diabetes Study). All participants were of 100% Japanese ancestry and were either second- or third-generation American immigrants. Previous reports provide greater detail on the identification, selection, and recruitment of these research subjects [21]. In brief, recruitment was conducted within the Japanese American community in the geographic area of King County, Washington, USA. Resources used to identify potential participants included a comprehensive mailing list and telephone directory resources, which together captured approximately 95% of the target population. Participants were prospectively followed to assess changes in research measurements of interest related to health status, with follow-up assessments performed 5 to 6 years and 10 to 11 years after the baseline assessment. The University of Washington Human Subjects Division approved this study, and all subjects provided written informed consent (Institutional Review Board number: 34469).

Among 425 potential subjects, 126 were excluded due to hypertension at baseline. Additional subjects were excluded for the following reasons: usage of lipid-lowering medications (n=3), missing computed tomography (CT) measurements of abdominal fat at baseline (n=8), and failure to return for or to complete follow-up assessments (n=55). Thus, data on a total of 233 subjects without hypertension at baseline were included in this report.

**Clinical and laboratory examination**

Research procedures were performed at the General Clinical Research Center at the University of Washington. The initial baseline assessment included a physical examination, as well as the use of a standard research questionnaire to obtain a past medical history and information regarding lifestyle, personal, and social characteristics and current medication use. Following a 30-minute rest period, the subject was placed in the recumbent position, and a mercury sphygmomanometer was employed to measure BP to the nearest 2 mm Hg. A total of three consecutive measurements of BP were performed, with the result calculated as the mean of the last two measurements. Hypertension was defined as a measured systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or as current treatment with an antihypertensive medication. Smoking status was assessed, and subjects were dichotomously classified as current or never/past smokers. Alcohol consumption was also dichotomously classified as at least 6 g of ethanol per day or less than 6 g per day [22]. The Paffenbarger physical activity index instrument was used to estimate the amount of kilocalories typically spent being physical-
ly active each week [23], with regular physical activity defined as weekly activities of moderate intensity or greater. Examples of physical activities of moderate or greater intensity in this index include jogging, swimming, playing tennis, gardening, active training for sports such as soccer, and heavy manual labor such as mining or working as a lumberjack.

Blood was collected following an overnight 10-hour fast. The definition of diabetes mellitus was based on American Diabetes Association criteria that included 75-g oral glucose tolerance testing [24]. An autoanalyzer that employed the hexokinase method (Department of Laboratory Medicine, University of Washington, Seattle, WA, USA) was used to measure plasma glucose levels. A radioimmunoassay measurement of plasma insulin was performed at the Diabetes Research Center at the University of Washington. The homeostasis model assessment of insulin resistance (HOMA-IR) index was used as a proxy measure of insulin sensitivity and was calculated as (fasting serum insulin [mIU/mL] × fasting serum glucose [mmol/L]) / 22.5 [25]. Levels of total cholesterol, triglycerides, and HDL cholesterol were measured according to the modified procedures of the Lipid Research Clinics, and levels of apolipoproteins B and A-1 were determined using radioimmunoassays (Northwest Lipid Research Laboratory, University of Washington, Seattle, WA, USA).

Single (1-cm) CT scan slices were obtained of the abdomen at the level of the umbilicus as detailed previously [26]. The abdominal visceral and subcutaneous fat areas were measured using density contour software.

### Statistical analysis
Continuous measurements were represented as mean ± standard deviation (SD), and discrete or categorical measurements were reported as numbers and percentages. Statistical differences between means of continuous measurements were evaluated using the independent *t* test, while categorical data were analyzed using the chi-square test. Multiple logistic regression analysis was used to identify independent associations between baseline plasma apoB concentrations and incident hypertension over 10 years.

| Characteristic                          | Total (n=233) | Normotensive at follow-up (n=183) | Hypertensive at follow-up (n=50) | P value |
|----------------------------------------|--------------|-----------------------------------|----------------------------------|--------|
| Age, yr                                | 46.4±11.0    | 45.1±10.4                         | 51.1±11.9                        | 0.002  |
| Female sex                             | 156 (67.0)   | 119 (65.0)                        | 37 (74.0)                        | 0.232  |
| BMI, kg/m²                             | 23.4±3.2     | 23.1±3.2                          | 24.1±3.3                        | 0.059  |
| Systolic BP, mm Hg                     | 119.3±10.1   | 117.1±9.4                         | 126.2±9.4                       | <0.001 |
| Diastolic BP, mm Hg                    | 72.4±7.4     | 71.4±7.4                          | 76.0±6.1                        | <0.001 |
| Current smoker                         | 36 (15.5)    | 30 (16.4)                         | 6 (12.0)                         | 0.446  |
| Moderate or higher alcohol consumption | 42 (18.0)    | 34 (18.6)                         | 8 (16.0)                         | 0.674  |
| Regular physical activity              | 48 (20.6)    | 40 (21.9)                         | 8 (16.0)                         | 0.364  |
| Diabetes mellitus                      | 21 (9.0)     | 12 (6.6)                          | 9 (18.0)                         | 0.012  |
| Fasting plasma glucose, mg/dL          | 90.6±15.0    | 88.6±11.1                         | 98.2±23.1                       | 0.006  |
| Fasting insulin, μU/mL                 | 13.2±6.3     | 12.8±6.2                          | 14.8±6.2                        | 0.045  |
| HOMA-IR                                | 3.00±1.67    | 2.83±1.57                         | 3.63±1.85                       | 0.003  |
| Total cholesterol, mg/dL               | 218±36       | 214±34                            | 231±40                          | 0.002  |
| Triglycerides, mg/dL                   | 119±109      | 119±119                           | 119±57                          | 0.991  |
| HDL-C, mg/dL                           | 63±17        | 63±18                             | 60±15                           | 0.156  |
| ApoB, g/L                              | 1.08±0.26    | 1.04±0.23                         | 1.22±0.29                       | <0.001 |
| ApoA-1, g/L                            | 1.55±0.32    | 1.54±0.30                         | 1.57±0.37                       | 0.498  |
| Abdominal visceral fat area, cm²       | 61.4±38.4    | 56.5±37.9                         | 79.4±35.1                       | <0.001 |
| Abdominal subcutaneous fat area, cm²   | 160.9±78.2   | 150.4±76.9                        | 199.6±71.0                      | <0.001 |

Values are expressed as mean ± standard deviation or number (%). BMI, body mass index; BP, blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein cholesterol; apo, apolipoprotein.
years while adjusting for covariates. Odds ratios (ORs) were obtained from coefficients for independent variables in the logistic regression models, and 95% confidence intervals (CIs) were estimated. ORs for independent variables were calculated using 1-SD increments. The presence of effect modification was tested via the insertion of first-order interaction terms into the regression models. Data analysis was performed using the IBM SPSS Statistics for Windows version 22.0 software package (IBM Corp., Armonk, NY, USA). The threshold for statistical significance was set at a two-sided $P$ value $<0.05$.

**RESULTS**

At baseline, study participants had a mean age of 46.4 years and a mean body mass index (BMI) of 23.4 kg/m$^2$, and 33.0% were men (Table 1). Over a 10-year follow-up period, 50 of the 233 participants (21.5%) developed hypertension. At baseline, those who later developed hypertension tended to be older and to have higher systolic BP, diastolic BP, HOMA IR, and levels of fasting plasma glucose, total cholesterol, and apoB than those who did not develop hypertension. With regard to lifestyle factors that may affect hypertension risk, no differences were observed in smoking status, alcohol consumption, and physical activity between the two groups. Although BMI was similar between the two groups, subjects who developed hypertension had significantly larger abdominal visceral and subcutaneous fat areas than subjects who did not.

In the univariate logistic regression analysis, age, BP, diabetes mellitus status, fasting plasma glucose level, fasting insulin level, HOMA-IR, and abdominal visceral and subcutaneous fat areas were associated with the incidence of hypertension (Table 2). In addition, levels of total cholesterol and apoB, but not triglycerides, HDL cholesterol, or apolipoprotein A1, showed positive associations with the development of hypertension.

We next examined multivariable models to determine whether baseline apoB concentration independently predicted incident hypertension over 10 years of follow-up. We found that apoB levels were independently associated with the odds of future hypertension after adjustment for age, sex, BMI, systolic BP,

### Table 2. Unadjusted Relative Odds of Incident Hypertension

| Variable                        | OR (95% CI)   | $P$ value |
|---------------------------------|---------------|-----------|
| Age                             | 1.66 (1.23–2.25) | 0.001     |
| Female sex                      | 1.53 (0.76–3.09) | 0.234     |
| BMI                             | 1.34 (0.99–1.82) | 0.061     |
| Systolic BP                     | 2.92 (1.96–4.37) | $<0.001$ |
| Diastolic BP                    | 2.08 (1.42–3.05) | $<0.001$ |
| Current smoking                 | 0.70 (0.27–1.78) | 0.448     |
| Moderate alcohol consumption    | 0.84 (0.36–1.94) | 0.674     |
| Regular physical activity       | 0.68 (0.30–1.57) | 0.366     |
| Diabetes mellitus               | 3.13 (1.24–7.92) | 0.016     |
| Fasting plasma glucose          | 1.84 (1.26–2.68) | 0.002     |
| Fasting insulin                 | 1.34 (1.00–1.80) | 0.048     |
| HOMA-IR                         | 1.53 (1.14–2.04) | 0.004     |
| Total cholesterol               | 1.64 (1.18–2.26) | 0.003     |
| Triglycerides                   | 1.00 (0.73–1.37) | 0.991     |
| HDL-C                           | 0.79 (0.56–1.10) | 0.156     |
| ApoB                            | 2.07 (1.47–2.90) | $<0.001$ |
| ApoA-I                          | 1.11 (0.82–1.51) | 0.497     |
| Abdominal visceral fat area      | 1.76 (1.29–2.40) | $<0.001$ |
| Abdominal subcutaneous fat area  | 1.84 (1.34–2.54) | $<0.001$ |

ORs for continuous variables reflect a 1-standard deviation increase. OR, odds ratio; CI, confidence interval; BMI, body mass index; BP, blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein cholesterol; apo, apolipoprotein.

### Table 3. Multivariate Logistic Regression Analysis of the Odds of Incident Hypertension at 10-Year Follow-up in Relation to ApoB Concentration at Baseline

| Model | Variables included in the model | OR (95% CI) | $P$ value |
|-------|---------------------------------|-------------|-----------|
| Model 1| Age, sex, BMI, and systolic BP   | 1.73 (1.15–2.61) | 0.008     |
| Model 2| Model 1 variables+HOMA-IR       | 1.72 (1.14–2.59) | 0.009     |
| Model 3| Model 1 variables+abdominal visceral and subcutaneous fat areas | 1.73 (1.15–2.62) | 0.009     |
| Model 4| Model 1 variables+HOMA-IR+abdominal visceral and subcutaneous fat areas | 1.73 (1.15–2.62) | 0.009     |
| Model 5| Model 4 variables+total cholesterol+diabetes mellitus | 1.89 (1.06–3.37) | 0.030     |

ORs for continuous variables reflect a 1-standard deviation increase. apo, apolipoprotein; OR, odds ratio; CI, confidence interval; BMI, body mass index; BP, blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance.
and abdominal visceral and subcutaneous fat areas (Table 3, model 4). The relationship between apoB and hypertension remained significant when further adjusted for total cholesterol level, diabetes status, and HOMA-IR (Table 3, model 5). We examined the first-order interaction term between apoB and sex in the prediction of incident hypertension in model 5 of Table 3, but found it to not be statistically significant (interaction term coefficient, −0.723; P = 0.130).

A subgroup analysis was performed among participants without diabetes by excluding the 21 subjects with this diagnosis and repeating the analyses that generated model 5 from Table 3. Baseline apoB concentration remained a significant independent predictor of hypertension over 10 years in this subgroup analysis (model 5: OR per 1-SD increase, 2.43; 95% CI, 1.29 to 4.59; P = 0.006).

DISCUSSION

These prospective data showed that a greater baseline apoB concentration was independently associated with a higher risk of incident hypertension over 10 years in Japanese Americans. The association between baseline apoB concentration and incident hypertension over 10 years could not be explained by overall or abdominal adiposity measures, glycemia, insulin sensitivity, total cholesterol level, or demographic factors included in regression models as covariates.

Previous prospective studies of the relationship between apoB concentrations and the future development of hypertension have reported findings consistent with ours, but those studies did not adjust for visceral adiposity as measured by imaging and inconsistently adjusted for insulin sensitivity. In the Women’s Health Study, which consisted of mostly Caucasian women followed for 8 years, higher apoB levels were found to be associated with a greater risk of hypertension [15]. As this result was not adjusted for central adiposity or insulin sensitivity, it does not provide evidence for an independent association between apoB levels and the development of hypertension. In a 5.9-year follow-up of middle-aged and elderly Turkish subjects, apoB concentrations were found to be associated with new-onset hypertension after adjustment for waist circumference in women, but this relationship was not found in men [13]. However, a study of middle-aged Finnish men during a 7-year follow-up period showed that apoB concentrations predicted the onset of hypertension independently of waist circumference and fasting insulin level [14]. In addition, in young Finnish men and women, apoB levels predicted incident hypertension over 6 years independently of HOMA-IR [16].

The present study differs from the aforementioned ones in the following respects. First, we included both men and women, and we did not find a significant interaction between sex and apoB levels. Our results therefore apply to both sexes. Second, we adjusted for abdominal visceral and subcutaneous fat areas as quantified by CT scans. This is a more accurate method of measuring abdominal fat distribution than is waist circumference, as the latter cannot be used to distinguish between fat accumulation in the visceral or abdominal subcutaneous depots and typically demonstrates only a moderate correlation with visceral fat as measured by imaging [27]. Third, this is the first prospective Asian population-based study to demonstrate an independent role of apoB levels in predicting incident hypertension.

Visceral adiposity is known to be associated with both insulin resistance and increased hepatic apoB secretion due to greater delivery of free fatty acids to the liver via the portal vein [28]. Cross-sectional research has shown plasma apoB concentrations to be strongly correlated with abdominal visceral fat accumulation [17]. Therefore, it is plausible that the relationship between high apoB concentration and incident hypertension may be mediated by the accumulation of visceral fat. However, based on our data, the presence of an association between hypertension and high plasma apoB concentrations independently of visceral adiposity and insulin resistance suggests a separate role for apoB in the pathogenesis of hypertension. Therefore, plasma apoB level has the potential to be valuable in the identification of persons at relatively high risk of hypertension, and research into its pathogenesis is likely warranted.

Current biological information suggests several potential mechanisms by which a high apoB concentration may result in hypertension. First, the infiltration and retention of apoB-containing lipoproteins in the arterial wall is a critical initiating event that sparks an inflammatory response and promotes endothelial dysfunction and the development of hypertension [29]. Plasma apoB concentrations have been found to be inversely associated with flow-mediated vasodilation, a widely-used measure of endothelial dysfunction in both healthy and obese individuals with type 2 diabetes [16,30]. Second, apoB has a pathogenic role in the development of atherosclerosis. Research has demonstrated that direct interaction between apoB and proteoglycans in the subendothelial space initiates an early stage of atherosclerosis [31]. Progressive atherosclerosis can result in structural changes in large arteries, leading to BP elevation [32]. Third, inflammation due to increased apoB concentrations can
lead to hypertension. Elevated apoB levels have been found to be associated with higher concentrations of inflammatory markers such as C-reactive protein TNF-α, interleukin-6 [33]. These inflammatory response shown to be possibly involved in the pathogenesis of hypertension [34]. However, previous research has also shown that apoB concentration predicts the incidence of hypertension independently of the C-reactive protein level, thereby diminishing the likelihood of an inflammatory mechanism explaining this association [13,16].

The associations between apoB levels and inflammation, endothelial function, and atherosclerosis suggest potential utility for the measurement of apoB in the prediction of cardiovascular disease risk. Importantly, apoB measurement is widely available, standardized, and automated, and it can be carried out with excellent precision on fresh or frozen samples [35]. Furthermore, as the measurement of apoB levels does not require fasting, it is more convenient than other lipid profiles that may require a fast.

The strengths of our study include subjects from a well-conducted community-based cohort with a long-term follow-up duration, imaging studies of body composition, and detailed measurements of lipid and glucose metabolism. The prospective design of this study permitted measurement of apoB levels prior to the outcome assessment, thereby establishing temporal sequence to permit better assessment of potential causality, which is not possible in most cross-sectional research. However, our study has some potential limitations. First, the findings are from Japanese Americans of 100% Japanese ancestry, and it is unknown whether these results can be applied to other ethnic groups. Second, BP was measured with a standard protocol in the recumbent position, but current guidelines advise its measurement in the sitting position [36]. Third, the number of participants was relatively small; nevertheless, the study was adequately powered to detect several significant predictors of incident hypertension. Lastly, inflammatory markers were not measured in this study. Hence, we were unable to explore whether such markers may mediate the association between apoB level and hypertension.

In summary, high plasma apoB concentrations predicted future hypertension in Japanese Americans after adjustment for conventional cardiovascular disease risk factors, direct measurements of abdominal fat depots, and insulin sensitivity as measured by HOMA-IR. These results provide a valuable perspective in understanding the association between apoB levels and hypertension by demonstrating the independence of this association from several other factors associated with both lipid concentrations and hypertension risk. Further research is required to confirm this association in other racial and ethnic groups and to better understand the pathophysiological mechanisms linking apoB levels and incident hypertension.

CONFLICTS OF INTEREST

The authors report no conflicts of interest in this work with one exception: Edward J. Boyko participated on an advisory committee of Bayer AG.

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AUTHOR CONTRIBUTIONS

Conception or design: S.J.H., E.J.B. Acquisition, analysis, or interpretation of data: S.J.H., E.J.B. Drafting the work or revising: S.J.H., W.Y.F., S.E.K., D.L.L., E.J.B. Final approval of the manuscript: S.J.H., W.Y.F., S.E.K., D.L.L., E.J.B.

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