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

pathogenesis [5,6]. Dyslipidemia is characterized by elevated levels of triglycerides, apolipoprotein B (apoB), and small low-density lipoprotein (LDL) particles and by reduced levels of high-density lipoprotein (HDL) cholesterol and apolipoprotein A1 [7].

The plasma apoB concentration is a direct measure of the total number of circulating atherogenic particles, including LDL, intermediate-density lipoprotein, and very low-density lipoprotein cholesterol, as well as lipoprotein(a) [8]. Several epidemiological studies and randomized controlled trials have shown that apoB concentration is a better marker of cardiovascular disease risk and response to lipid-lowering therapy than LDL cholesterol level [9-11].

In some cross-sectional studies, plasma apoB concentrations have been found to be significantly associated with hypertension [3,4,12]. Whether a causal relationship exists between plasma apoB levels and hypertension is not clear from the published cross-sectional observational research. To date, a few prospective studies have investigated the association between apoB concentrations and the development of hypertension [13-16]. However, these prospective studies had limitations, such as the inclusion of either only women or only men, the inclusion of only young participants, or potential diagnostic inaccuracy due to the use of a self-reported diagnosis of hypertension.

Disturbances in apoB metabolism are strongly associated with visceral adiposity and insulin resistance, as apoB levels are positively correlated with the size of the visceral adipose depot and inversely correlated with insulin sensitivity [17]. Previous reports from the Japanese American Community Diabetes Study have shown that greater visceral adiposity is related to both the prevalence and the incidence of hypertension [18-20]. However, the possibility exists that higher apoB concentrations may merely serve as a marker of greater visceral fat area and insulin resistance and have no independent association with hypertension.

To our knowledge, no prospective study of the association between apoB and incident hypertension has adjusted for directly-measured abdominal fat depots and insulin sensitivity. Therefore, we examined the relationship between baseline plasma apoB concentrations and the incidence of hypertension over 10 years in a Japanese American cohort of men and women in whom these measures were quantified.

METHODS

Study subjects

The study population was selected from participants in a pro-

spective 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 choles-

terol 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

Table 1. Baseline Characteristics of Subjects by Incident Hypertension at 10-Year Follow-up

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/m², 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-1	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

ACKNOWLEDGMENTS

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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REFERENCES

1. Ferdinand KC, Kleinpeter MA. Management of hypertension and dyslipidemia. Curr Hypertens Rep 2006;8:489-96.
2. Bønaa KH, Thelle DS. Association between blood pressure and serum lipids in a population. The Tromso Study. Circulation 1991;83:1305-14.
3. Cicero AF, D'Addato S, Veronesi M, Rosticci M, Santi F, Dormi A, et al. Relationship between blood pressure, cholesterolemia and serum apolipoprotein B in a large population

sample: the Brisighella Heart Study. J Hypertens 2012; 30:492-6.

4. Borghi C, Rodriguez-Artalejo F, De Backer G, Dallongeville J, Medina J, Guallar E, et al. The association between blood pressure and lipid levels in Europe: European Study on Cardiovascular Risk Prevention and Management in Usual Daily Practice. J Hypertens 2016;34:2155-63.

5. Boyko EJ, Doheny RA, McNeely MJ, Kahn SE, Leonetti DL, Fujimoto WY. Latent class analysis of the metabolic syndrome. Diabetes Res Clin Pract 2010;89:88-93.

6. Carr DB, Utzschneider KM, Hull RL, Kodama K, Retzlaff BM, Brunzell JD, et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. Diabetes 2004;53:2087-94.

7. Ginsberg HN, Zhang YL, Hernandez-Ono A. Metabolic syndrome: focus on dyslipidemia. Obesity (Silver Spring) 2006;14 Suppl 1:41S-9S.

8. Morita SY. Metabolism and modification of apolipoprotein B-containing lipoproteins involved in dyslipidemia and atherosclerosis. Biol Pharm Bull 2016;39:1-24.

9. Sniderman AD, Williams K, Contois JH, Monroe HM, McQueen MJ, de Graaf J, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. Circ Cardiovasc Qual Outcomes 2011;4:337-45.

10. Pedersen TR, Olsson AG, Faergeman O, Kjekshus J, Wedel H, Berg K, et al. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). Circulation 1998;97:1453-60.

11. Simes RJ, Marschner IC, Hunt D, Colquhoun D, Sullivan D, Stewart RA, et al. Relationship between lipid levels and clinical outcomes in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels? Circulation 2002;105: 1162-9.

12. Okosun IS, Choi S, Hash R, Dever GE. Apolipoprotein B, ratio of total cholesterol to HDL-C, and blood pressure in abdominally obese white and black American women. J Hum Hypertens 2001;15:299-305.

13. Onat A, Can G, Hergenc G, Yazici M, Karabulut A, Albayrak S. Serum apolipoprotein B predicts dyslipidemia, metabolic syndrome and, in women, hypertension and diabetes, independent of markers of central obesity and inflam-

mation. Int J Obes (Lond) 2007;31:1119-25.

14. Laaksonen DE, Niskanen L, Nyyssonen K, Lakka TA, Laukkanen JA, Salonen JT. Dyslipidaemia as a predictor of hypertension in middle-aged men. Eur Heart J 2008;29: 2561-8.

15. Paynter NP, Sesso HD, Conen D, Otvos JD, Mora S. Lipoprotein subclass abnormalities and incident hypertension in initially healthy women. Clin Chem 2011;57:1178-87.

16. Koskinen J, Magnussen CG, Wurtz P, Soininen P, Kangas AJ, Viikari JS, et al. Apolipoprotein B, oxidized low-density lipoprotein, and LDL particle size in predicting the incidence of metabolic syndrome: the Cardiovascular Risk in Young Finns study. Eur J Prev Cardiol 2012;19:1296-303.

17. Despres JP, Lamarche B. Effects of diet and physical activity on adiposity and body fat distribution: implications for the prevention of cardiovascular disease. Nutr Res Rev 1993;6:137-59.

18. Hayashi T, Boyko EJ, Leonetti DL, McNeely MJ, Newell-Morris L, Kahn SE, et al. Visceral adiposity and the prevalence of hypertension in Japanese Americans. Circulation 2003;108:1718-23.

19. Hayashi T, Boyko EJ, Leonetti DL, McNeely MJ, Newell-Morris L, Kahn SE, et al. Visceral adiposity is an independent predictor of incident hypertension in Japanese Americans. Ann Intern Med 2004;140:992-1000.

20. Sullivan CA, Kahn SE, Fujimoto WY, Hayashi T, Leonetti DL, Boyko EJ. Change in intra-abdominal fat predicts the risk of hypertension in Japanese Americans. Hypertension 2015;66:134-40.

21. Fujimoto WY, Leonetti DL, Kinyoun JL, Shuman WP, Stolov WC, Wahl PW. Prevalence of complications among second-generation Japanese-American men with diabetes, impaired glucose tolerance, or normal glucose tolerance. Diabetes 1987;36:730-9.

22. Koppes LL, Dekker JM, Hendriks HF, Bouter LM, Heine RJ. Moderate alcohol consumption lowers the risk of type 2 diabetes: a meta-analysis of prospective observational studies. Diabetes Care 2005;28:719-25.

23. Paffenbarger RS Jr, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. Am J Epidemiol 1978;108:161-75.

24. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004;27 Suppl 1:S5-10.

25. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment:

insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.

26. Shuman WP, Morris LL, Leonetti DL, Wahl PW, Moceri VM, Moss AA, et al. Abnormal body fat distribution detected by computed tomography in diabetic men. Invest Radiol 1986;21:483-7.

27. Janssen I, Heymsfield SB, Allison DB, Kotler DP, Ross R. Body mass index and waist circumference independently contribute to the prediction of nonabdominal, abdominal subcutaneous, and visceral fat. Am J Clin Nutr 2002;75:683-8.

28. Riches FM, Watts GF, Naoumova RP, Kelly JM, Croft KD, Thompson GR. Hepatic secretion of very-low-density lipoprotein apolipoprotein B-100 studied with a stable isotope technique in men with visceral obesity. Int J Obes Relat Metab Disord 1998;22:414-23.

29. Feingold KR, Anawalt B, Boyce A. Endotext. Dartmouth: MDText.com Inc.; 2000. Chapter, The role of lipids and lipoproteins in atherosclerosis. Available from: https://www.ncbi.nlm.nih.gov/books/NBK343489/.

30. Rasmussen JG, Eschen RB, Aardestrup IV, Dethlefsen C, Griffin BA, Schmidt EB. Flow-mediated vasodilatation: variation and interrelationships with plasma lipids and lipoproteins. Scand J Clin Lab Invest 2009;69:156-60.

31. Skalen K, Gustafsson M, Rydberg EK, Hulten LM, Wiklund O, Innerarity TL, et al. Subendothelial retention of atherogenic lipoproteins in early atherosclerosis. Nature 2002;417:750-4.

32. Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. Ann Intern Med 2003;139:761-76.

33. Faraj M, Messier L, Bastard JP, Tardif A, Godbout A, Prud'homme D, et al. Apolipoprotein B: a predictor of inflammatory status in postmenopausal overweight and obese women. Diabetologia 2006;49:1637-46.

34. De Miguel C, Rudemiller NP, Abais JM, Mattson DL. Inflammation and hypertension: new understandings and potential therapeutic targets. Curr Hypertens Rep 2015;17:507.

35. Chan DC, Watts GF. Apolipoproteins as markers and managers of coronary risk. QJM 2006;99:277-87.

36. Muntner P, Shimbo D, Carey RM, Charleston JB, Gaillard T, Misra S, et al. Measurement of blood pressure in humans: a scientific statement from the American Heart Association. Hypertension 2019;73:e35-66.