High-density lipoprotein cholesterol is positively associated with hypertension in apparently healthy Japanese men and women

E. ODA and R. KAWAI
Medical Check-Up Center, Tachikawa Medical Center
Nagacho 2-2-16, Nagaoka, Niigata, 940-0053, Japan

Accepted: 27 July 2010

ABSTRACT

Among five components of metabolic syndrome, high-density lipoprotein (HDL) cholesterol is unique because it is not significantly associated with blood pressure. This study looks at cross-sectional relationships between HDL cholesterol and hypertension using medical check-up data from 1803 apparently healthy Japanese men aged 49.9±9.0 years, and 1150 Japanese women aged 49.5±9.0 years. Pearson's correlation coefficients between systolic blood pressure (SBP)/diastolic blood pressure (DBP) and HDL cholesterol were –0.01 (ns)/–0.01 (ns) in men and –0.04 (ns)/–0.01 (ns) in women. The standardised partial regression coefficient of HDL cholesterol for SBP/DBP (mmHg) controlling for age, body mass index (BMI), fasting plasma glucose (FPG), triglycerides, high-sensitivity C-reactive protein (hs-CRP) and low-density lipoprotein (LDL) cholesterol were 0.15 ($P<0.0001$)/0.15 ($P<0.0001$) in men and 0.10 ($P<0.0001$)/0.12 ($P<0.0001$) in women. The odds ratio (OR; 95% confidence interval [CI]) of a 1mg/dL increment of HDL cholesterol for hypertension controlling for age, BMI, FPG, triglycerides, hs-CRP, LDL cholesterol, metabolic syndrome, diabetes, exercise status, drinking status, and smoking status was 1.03 (1.02–1.04; $P<0.001$) in men and 1.03 (1.01–1.05; $P=0.002$) in women. Thus, HDL cholesterol was independently positively associated with hypertension in apparently healthy Japanese men and women.

KEY WORDS: Blood pressure.
Cholesterol, HDL.
Hypertension.
Metabolic syndrome.

Introduction

Insulin resistance syndrome[1] or metabolic syndrome (MetS)[2–7] represents interrelated metabolic risk factors that appear to promote the development of diabetes and cardiovascular disease. Established components of MetS are increased waist circumference, high blood pressure, increased serum triglyceride level, decreased serum high-density lipoprotein (HDL) cholesterol levels, and impaired fasting glucose.[2–6]

Recently, a worldwide consensus statement[6] for harmonising MetS criteria was issued jointly by the International Diabetes Federation (IDF) Task Force on Epidemiology and Prevention, the National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, and the International Association for the Study of Obesity. Thus, the revised National Cholesterol Education Program (NCEP) criteria[4] where abdominal obesity is not a necessary component of MetS was adopted as the worldwide definition of MetS, and the IDF criteria of MetS[5] where abdominal obesity is a necessary component was withdrawn.[6]

Increased serum levels of high-sensitivity C-reactive protein (hs-CRP)[8–12] and fatty liver disease[13] are reported as associated components of MetS. Previously, associations have been reported between MetS and high-sensitivity C-reactive protein (hs-CRP),[9–12] low-density lipoprotein (LDL) cholesterol,[14] uric acid,[15] vital capacity,[16,17] heart rate[18] and liver function tests[19] in Japanese.

Hypertriglyceridaemia and hypo-HDL cholesterolaemia (known as dyslipidaemia) cause endothelial dysfunction and the loss of physiological vasomotor activity that results from endothelial dysfunction may lead to increased blood pressure. A study in the USA reported that men in the highest quintile of HDL cholesterol had a decreased risk of developing hypertension compared with those in the lowest quintile.[20] However, among five components of MetS, HDL cholesterol is unique because it does not significantly correlate with blood pressure. Thus, the relationship between HDL cholesterol and hypertension may be controversial.

This study investigates the cross-sectional relationships between HDL cholesterol and hypertension using medical check-up data from apparently healthy Japanese men and women.

Subjects and methods

Subjects

Between 1 April 2008 and 31 March 2009, 2541 men and 1502 women visited the medical check-up centre for general health screening. Visitors were all required to fill out a

Correspondence to: Eiji Oda
Email: ijie@venus.sannet.ne.jp

questionnaire on the history of stroke and ischaemic heart disease, exercise, smoking and drinking status, and antihypertensive, antidiabetic, and antihyperlipidaemic medication. Among them, 1803 men (aged 49.9±9.0 years) and 1150 women (aged 49.5±9.0 years), all apparently healthy, were recruited to the present study. None had a history of cardiovascular disease or stroke, diabetes, or were on antihypertensive and/or antihyperlipidaemic medication. The study protocol was approved by the ethics committee at Tachikawa Medical Center and informed consent was obtained from each subject.

Measurements

After an overnight fast, blood samples were obtained for routine medical check-up tests: fasting plasma glucose (FPG), triglycerides, HDL cholesterol, LDL cholesterol and hs-CRP. Chemical measurements were performed at BML Nagaoka (Nagaoka, Japan) with routine laboratory methods. High-sensitivity CRP was measured at BML General Laboratory (Tokyo, Japan) with nephelometry using N-latex CRP-2 (Siemens Healthcare Japan, Tokyo, Japan). The measurement limit of hs-CRP was 0.02 mg/L and the hs-CRP value less than the measurement limit was considered as 0.01 mg/L. LDL cholesterol was measured by a direct surfactant method using Choletest-LDL (Sekisui Medical, Tokyo, Japan). Percentage body fat (%BF) was measured by bioelectrical impedance analysis using TBF-210 (TANITA, Tokyo, Japan). Average systolic blood pressure (SBP) and diastolic blood pressure (DBP) was calculated from two measurements taken with the subject in a sitting position after 5 min rest. Waist circumference (WC) was measured at the level of the umbilicus. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres.

Definitions

Metabolic syndrome was defined by revised NCEP criteria[1,3] as three or more of five components where the cut-off point of WC was modified for Japanese as ≥90 cm in men and ≥80 cm in women according to IDF recommendations.[2] Diabetes was defined as fasting glucose ≥126 mg/dL and/or with antidiabetic medication, and hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg. Exercisers were defined as subjects who walked at least one hour per day or who exercised for 30 min or more at least twice a week.

Statistical analysis

Pearson's correlation coefficients for obesity indices and metabolic risk factors were calculated. Stepwise linear regression adopting $P>0.1$ as an excluding criterion and SBP/DBP as a dependent variable, and age, BMI, FPG, triglycerides, HDL cholesterol, hs-CRP, and LDL cholesterol as initial independent variables were performed. Stepwise

Table 1. Basal data.

	Men (n=1803)	Women (n=1150)
Age (years)	49.9±9.0	49.5±9.0
Body mass index (kg/m^2)	23.0±2.8	21.5±3.0
Waist circumference (cm)	83.6±7.8	78.1±8.2
Body fat (%)	21.8±5.0	26.5±5.7
Systolic blood pressure (mmHg)	120.1±16.9	110.2±15.8
Diastolic blood pressure (mmHg)	76.3±10.4	68.8±9.7
Fasting plasma glucose (mg/dL)	94.5±13.8	88.3±8.6
Triglycerides (mg/dL)	121.8 (101)±77.5	79.4 (69)±45.2
HDL cholesterol (mg/dL)	57.7±14.4	68.0±14.6
High-sensitivity CRP (mg/L)	0.66 (0.29)±1.60	0.45 (0.21)±0.82
LDL cholesterol (mg/dL)	122.5±29.8	120.6±30.5
Prevalence		
Exercisers	35.6	34.9
Current smokers	36.6	6.7
Regular drinkers	51.9	15.3
Metabolic syndrome	11.1	4.4
Diabetes	2.3	0.5
Hypertension	14.5	5.5

Values are mean (median)±SD or %

Table 2. Pearson's correlation coefficients among metabolic risk factors.

	BMI	WC	%BF	SBP	DBP	FPG	LnTG	HDLc	LnCRP	LDLc
BMI		0.85	0.92	0.39	0.37	0.27	0.25	–0.27	0.31	0.26
WC	0.87		0.83	0.36	0.34	0.26	0.29	–0.27	0.32	0.29
%BF	0.82	0.81		0.38	0.35	0.27	0.27	–0.26	0.38	0.29
SBP	0.34	0.31	0.30		0.92	0.29	0.20	–0.04	0.20	0.19
DBP	0.31	0.30	0.29	0.93		0.27	0.20	–0.01	0.19	0.18
FPG	0.19	0.20	0.20	0.19	0.19		0.17	–0.11	0.13	0.18
LnTG	0.37	0.40	0.42	0.21	0.21	0.19		–0.40	0.25	0.31
HDLc	–0.37	–0.37	–0.36	–0.01	–0.01	–0.07	–0.47		–0.21	–0.21
LnCRP	0.37	0.39	0.40	0.18	0.17	0.12	0.28	–0.30		0.15
LDLc	0.27	0.27	0.33	0.06	0.05	0.09	0.25	–0.24	0.17	

BMI: body mass index, WC: waist circumference, %BF: percent body fat, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, LnTG: logarithmic transformation of triglycerides, HDLc: high-density lipoprotein cholesterol, LnCRP: logarithmic transformation of high-sensitivity C-reactive protein, LDLc: low-density lipoprotein cholesterol.
Male data (n=1803) are presented in the lower left triangle and female data (n=1150) are presented in the upper right triangle.

Table 3. Multiple linear regressions using blood pressure as a dependent variable.

		Systolic blood pressure (mmHg)			Diastolic blood pressure (mmHg)		
	Independent variables	PRC (95% CI)	SPRC	*P*	PRC (95% CI)	SPRC	*P*
Men	Age (years)	0.20 (0.12–0.28)	0.08	<0.0001	0.16 (0.12–0.21)	0.11	<0.0001
	BMI (kg/m²)	2.21 (1.95–2.48)	0.42	<0.000	1.27 (1.11–1.43)	0.38	<0.0001
	HDL cholesterol (mg/dL)	0.30 (0.25–0.34)	0.15	<0.0001	0.19 (0.16–0.22)	0.15	<0.0001
	FPG (md/dL)	0.13 (0.08–0.19)	0.11	<0.0001	0.08 (0.05–0.11)	0.10	<0.0001
	LnTG (mg/dL)	6.49 (5.18–7.80)	0.25	<0.0001	4.49 (3.68–5.30)	0.27	<0.0001
	LnCRP (mg/L)	0.73 (0.03–1.44)	0.01	0.04	0.39 (-0.04–0.82)	0.01	0.08
Women	Age (years)	0.20 (0.10–0.29)	0.09	<0.0001	0.08 (0.02–0.14)	0.06	0.005
	BMI (kg/m²)	1.81 (1.52–2.09)	0.35	<0.0001	1.05 (0.88–1.23)	0.33	<0.0001
	HDL cholesterol (mg/dL)	0.16 (0.11–0.21)	0.10	<0.0001	0.12 (0.09–0.15)	0.12	<0.0001
	FPG (md/dL)	0.36 (0.27–0.44)	0.28	<0.0001	0.21 (0.15–0.26)	0.26	<0.0001
	LnTG (mg/dL)	4.77 (3.06–6.47)	0.18	<0.0001	3.76 (2.70–4.82)	0.23	<0.0001
	LnCRP (mg/L)	0.75 (–0.01–1.51)	0.01	0.05	0.42 (-0.05–0.89)	0.01	0.08

PRC: partial regression coefficient, CI: confidence interval, SPRC: standardized PRC. Other abbreviations as for Table 2.

logistic regressions adopting $P>0.1$ as an excluding criterion, using hypertension as a dependent variable, and age, BMI, triglycerides, HDL cholesterol, hs-CRP, LDL cholesterol, MetS, diabetes, exercise status, smoking status and drinking status as initial independent variables were performed. Statistical analysis was performed using SPSS-2 (SPSS Japan, Tokyo). Triglycerides and hs-CRP were transformed to logarithms prior to calculation. $P<0.05$ was considered to be statistically significant.

Results

Basal data are presented in Table 1. Table 2 shows Pearson's correlation coefficients for metabolic risk factors. The correlation coefficients between SBP/DBP and HDL cholesterol were not significant. Table 3 shows multiple linear regressions using SBP/DBP as a dependent variable, and age, BMI, FPG, triglycerides, HDL cholesterol, hs-CRP and LDL cholesterol as initial independent variables. The standardised partial regression coefficients of HDL cholesterol for SBP/DBP (mmHg) were significant. Table 4 shows logistic regressions using hypertension as a dependent variable, and age, BMI, FPG, triglycerides, hs-CRP, LDL cholesterol, MetS, diabetes, exercise status, drinking status and smoking status as initial independent variables. The odds ratio (OD; 95% confidence interval [CI]) of a 1 mg/dL increment of HDL cholesterol for hypertension was 1.03 (1.02–1.04; $P<0.001$) in men and 1.03 (1.01–1.05; $P=0.002$) in women.

Discussion

Metabolic risk factors for MetS[1–7] generally correlate with correlation coefficients of approximately 0.2–0.4 (Table 2). However, HDL cholesterol and blood pressure do not correlate. In the present study, HDL cholesterol was positively associated with hypertension in apparently healthy Japanese men and women. These positive associations have not been reported previously, and the reason for this association is unclear. Medication and other therapeutic intervention may not be related to the association between HDL cholesterol and hypertension because subjects with antihypertensive and/or andihyperlipidaemic medication were excluded from the present study.

It is believed that metabolic risk factors correlate through underlying mechanisms such as increased adiposity,[5] insulin resistance,[1] low-grade systemic inflammation,[8–12,21] endothelial dysfunction[22] and autonomic dysfunction.[23] These mechanisms of MetS are associated with decreased serum HDL cholesterol level and increased blood pressure. Thus, the positive association between HDL cholesterol and blood pressure cannot be attributed to these underlying mechanisms. In the present study, smoking was negatively associated with hypertension in men (Table 4). It is well known that cigarette smoking is positively associated with triglycerides and negatively associated with HDL cholesterol in relation to insulin resistance.[24,25] Therefore, the positive association between HDL cholesterol and blood pressure may be partially mediated through cigarette smoking in men. However, cigarette smoking cannot explain the positive association between HDL cholesterol and blood pressure because the association between HDL cholesterol and blood pressure was independently controlled for smoking status, and the prevalence of smoking was only 6.7% in women, although the OR of HDL cholesterol for hypertension was 1.03 both in women and in men.

Alcohol increases serum HDL cholesterol level[26] and heavy drinking may increase blood pressure.[27,28] However, the association between HDL cholesterol and blood pressure was independently controlled for drinking status and, in the present study, moderate drinkers (50–79 g alcohol per day) represented just 15.3% of men and 1.6 % of women, while heavy drinkers (>80 g alcohol per day) represented only 2.7% of men and 0.2% of women. Therefore, it is unlikely that the positive association between HDL cholesterol and hypertension results from heavy drinking, especially in women. Thus, there may be unknown mechanisms responsible for the weak positive association between HDL cholesterol and blood pressure.

Cause and result relationships cannot be derived from the

Table 4. Logistic regressions using hypertension as a dependent variable.

Men			Women		
Independent variables	OR (95% CI)	*P*	Independent variables	OR (95% CI)	*P*
Metabolic syndrome (1, 0)	3.87 (2.55–5.89)	<0.0001	Metabolic syndrome (1, 0)	5.05 (2.09–12.17)	0.0003
Age (years)	1.03 (1.01–1.05)	0.0002	Age (years)	1.05 (1.01–1.08)	0.006
BMI (kg/m^2)	1.11 (1.04–1.17)	0.001	BMI (kg/m^2)	1.20 (1.11–1.31)	<0.0001
HDL cholesterol (mg/dL)	1.03 (1.02–1.04)	<0.0001	HDL cholesterol (mg/dL)	1.03 (1.01–1.05)	0.002
LnTG (mg/dL)	1.42 (1.03–1.96)	0.03	FPG (md/dL)	1.04 (1.02–1.07)	0.002
LnCRP (mg/L)	1.14 (0.99–1.32)	0.08	LnCRP (mg/L)	1.27 (0.96–1.69)	0.09
Current smoker (1, 0)	0.47 (0.34–0.66)	<0.0001	Constant	$3x10^{-7}$	<0.0001
Exercise (1, 0)	1.58 (1.19–2.10)	0.002			
Constant	0.0001	<0.0001			

Age, BMI, FPG, LnTG, HDL cholesterol, LnCRP, LDL cholesterol, metabolic syndrome, diabetes, exercise status, smoking status, and drinking status were used as initial independent variables. OR: odds ratio, CI: confidence interval. Other abbreviations as for Table 2.

present study. Halperin *et al*. reported that men in the highest quintile of HDL cholesterol had a 32% decreased risk of developing hypertension compared with those in the lowest quintile over a mean follow-up of 14.1 years.[20] There may be ethnic differences in the relationship between serum HDL cholesterol levels and incident hypertension. Some inhibitors of cholesteryl ester transfer protein increase serum HDL cholesterol levels, blood pressure and serum aldosterone levels.[29] Similar natural compounds may exist in some hypertensive patients.

It is possible that the increase in HDL cholesterol in hypertensive individuals is associated with an increased percentage of dysfunctional HDL. Furthermore, factors associated with hypertension (e.g., inflammation and oxidative stress) may contribute to disturbance of HDL metabolism and thus reduced recycling and renovation of HDL, resulting in higher serum HDL cholesterol levels. Some HDL particles in hypertensive individuals may not function to protect LDL from oxidation nor control cholesterol efflux from vascular walls. □

The authors thank all subjects who participated in the study, the paramedical staff who assisted with the study, and Dr. Shinpei Yoshii and Dr. Masaaki Okabe at Tachikawa Medical Center, and Professor Yoshifusa Aizawa at Niigata University Graduate School of Medical and Dental Sciences for their assistance.

References

1 Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988; **37**: 1595–607.
2 World Health Organization. *Definition, diagnosis, and classification of diabetes mellitus and its complications: report of a WHO Consultation*. Geneva: WHO, 1999.
3 Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486?97.
4 Grundy SM, Cleeman JI, Daniels SR *et al*. Diagnosis and management of the metabolic syndrome: a statement for health care professionals: an American Heart Association/National Heart, Lung and Blood Institute Scientific Statement. *Circulation* 2005; **112**: 2735–52.
5 Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome – a new worldwide definition. A consensus statement from the International Diabetes Federation. *Diabet Med* 2006; **23**: 469–80.
6 Alberti KGMM, Eckel RH, Grundy SM *et al.* Harmonizing the metabolic syndrome. A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; **120**: 1640–5.
7 Oda E. The metabolic syndrome as a concept of adipose tissue disease. *Hypertens Res* 2008; **31**: 1283–91.
8 Ridker PM, Wilson PWF, Grandy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? *Circulation* 2004; **109**: 2818–25.
9 Oda E, Oohara K, Abe A *et al*. The optimal cut-off point of C-reactive protein as an optional component of metabolic syndrome in Japan. *Circ J* 2006; **70**: 384–8.
10 Oda E, Kawai R. Very low levels of high-sensitivity C-reactive protein are not bimodally distributed but are significantly related to other metabolic risk factors in Japanese. *Intern Med* 2009; **48**: 953–8.
11 Oda E, Kawai R. Tentative cut-off point of high-sensitivity C-reactive protein for a component of metabolic syndrome in Japanese. *Circ J* 2009; **73**: 755–9.
12 Oda E, Kawai R. Reproducibility of high-sensitivity C-reactive protein as an inflammatory component of metabolic syndrome in Japanese. *Circ J* 2010; **74**: 1488–93.
13 Kotronen A, Yki-Järvinen H. Fatty liver: a novel component of the metabolic syndrome. *Arterioscler Thromb Vasc Biol* 2008; **28**: 27–38.
14 Oda E, Kawai R, Sukumaran V, Watanabe K. LDL cholesterol is more strongly associated with metabolic syndrome in Japanese women than in men. *Intern Med* 2009; **48**; 1607–14.
15 Oda E, Kawai R. Uric acid is positively associated with metabolic syndrome but negatively associated with diabetes in Japanese men. *Intern Med* 2009; **48**; 1607–14.
16 Oda E, Kawai R. A cross-sectional relationship between vital

capacity and diabetes in Japanese men. *Diabetes Res Clin Pract* 2009; **85**: 111–6.

17 Oda E, Kawai R. Low vital capacity is associated with diabetes despite inverse relationships with metabolic risk factors in lean Japanese men. *Intern Med* 2009; **48**: 1201–7.

18 Oda E, Kawai R. Significance of heart rate on the prevalence of metabolic syndrome and its related risk factors in Japanese. *Circ J* 2009; **73**: 1431–6.

19 Oda E, Kawai R, Watanabe, K, Sukumaran V. Prevalence of metabolic syndrome increases with the increase in blood levels of gamma glutamyltransferase and alanine aminotransferase in Japanese men and women. *Intern Med* 2009; **48**: 1343–50.

20 Halperin RO, Sesso HD, Ma J, Buring JE, Stampfer MJ, Gaziano JM. Dyslipidemia and the risk of incident hypertension in men. *Hypertension* 2006; **47**: 45–50.

21 Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes and inflammation. *Circulation* 2005; **111**: 1448–54.

22 Kim J, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction. Molecular and pathophysiological mechanisms. *Circulation* 2006; **113**: 1888–904.

23 Katagiri H, Yamada T, Oka Y. Adiposity and cardiovascular disorders: disturbance of the regulatory system consisting of humoral and neuronal signals. *Circ Res* 2007; **101**: 27–39.

24 Facchini FS, Hollenbeck CB, Jeppesen J, Chen YD, Reaven GM. Insulin resistance and cigarette smoking. *Lancet* 1992; **339**: 1128–30.

25 Farin HM, Abbasi F, Kim SH, Lamendola C, McLaughlin T, Reaven GM. The relationship between insulin resistance and dyslipidaemia in cigarette smokers. *Diabetes Obes Metab* 2007; **9**: 65–9.

26 Gaziano JM, Buring JE, Breslow JL *et al.* Moderate alcohol intake increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *N Engl J Med* 1993; **329**: 1829–34.

27 Fuchs FD, Chambless LE, Whelton PK, Nieto FJ, Heiss G.. Alcohol consumption and the incidence of hypertension: The Atherosclerosis Risk in the Communities Study. *Hypertension* 2001; **37**: 1242–50.

28 Sesso HD, Cook NR, Buring JE, Manson JE, Gaziano JM. Alcohol consumption and the risk of hypertension in women and men. *Hypertension* 2008; **51**: 1080–7.

29 Barter PJ, Caulfield M, Eriksson M *et al*. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007; **357**: 2109–22.