World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

CO-RRELATION OF DYSLIPIDEMIA WITH HYPERTENSION AND ITS CARDIAC OUTCOME-STUDY AT TERTIARY CARE HOSPITAL FROM CENTRAL INDIA

Premshanker Singh*[1], Ritu Karoli[2] and Mridu Singh[3]

[1]FMR Prof and Head Medicine, [2]Addl Prof Medicine, [3]Assoc Prof Medicine
Dept of Medicine, Dr RML Institute of Medical Sciences, Lucknow, India.

Corresponding Author: Dr. Premshanker Singh
FMR Prof and Head Medicine, Dept of Medicine, Dr RML Institute of Medical Sciences, Lucknow, India.

Article Received on 30/12/2021 **Article Revised on 20/01/2022** **Article Accepted on 10/02/2022**

ABSTRACT

Dyslipidemia and hypertension are the two widely recognized independent key risk factors for development of coronary vascular disorders (CVD). Therefore, Dyslipidemia and hypertension can serve as an easy clinical approach to know persons at greater risk and timely interference directed to decrease CVD events. Aim of study was to know correlation between dyslipidemia and hypertension and its cardiac outcome in a tertiary care hospital from central india. The present study was a prospective study conducted in the department of General Medicine in a tertiary care hospital at Lucknow, India-226010 over the period of two years from June 2017 to June2019. A total of HTN patients and 100 non hypertensive controls were recruited for the study. The patients were in the range of 35-75 years age group. Both known hypertensive patients who were on treatment for a varying period of time and newly diagnosed hypertensive patients were included in the study. The hypertensive and healthy controls were selected to the study by systematic random sampling. A structured and validated designed case report form (CRF) was used for data collection. The blood samples were drawn from all the patients after 12 hours of fasting. Fasting Blood Sugar(FBS), Postprandial blood sugar (PPBS) and Lipid profile values were obtained In conclusion, our findings show that elevated serum Total Cholesterol(TC),Low Density Lipoprotein Cholesterol (LDLC), and High Density Lipoprotein Cholesterol(HDLC) levels were associated with an increased risk of hypertension in working age Indian men.. Overall, our results may contribute to the accumulation of evidence that dyslipidemia increases risk of hypertension in Indian population. From a clinical perspective, the importance of strict BP management in patients with dyslipidemia was indicated Among 3554, hypertension patients 86% of them were males and 14% were females. Statistically significant difference was observed in total cholesterol, LDL cholesterol, TC/HDL ratio and LDL/HDL ratio between obese and non obese as well as in CVA, IHD among hypertensive patients relatively with healthy volunteers. Biochemically there was significant difference in total cholesterol, LDL cholesterol, TC/HDL ratio and LDL/HDL ratio between obese and non obese hypertensive patients.

INTRODUCTION

Hypertension and dyslipidemia are important risk factors for cardiovascular disease. Coexistence of hypertension and dyslipidemia is often observed in daily clinical practice and this empirical observation is consistent with baseline characteristics of clinical study participants[1,2,3,4] Population-based epidemiological studies have also reported that gradual increases in blood pressure (BP) or prevalence of hypertension are associated with increases in blood lipid levels[5,6,7,8] One possible explanation for these relationships is that hypertension and dyslipidemia share common pathophysiological etiologies, such as obesity and the resulting dysregulation of adipocytokine release from adipose tissue[9] Furthermore, dyslipidemia adversely affects functional and structural arterial properties and promotes atherosclerosis[10,11,12] These changes may impair BP regulation, which, in turn, predisposes individuals with dyslipidemia to development of hypertension. South Asian general populations wrap an elevated incidence of cardiovascular risk factors and earlier onset of cardiovascular disease (CVD) in spite of a normal body mass index as per international values.[13,14,15] Dyslipidemia and hypertension were the two widely recognized independent key risk factors for development of CVD[2,3,5,6] and these may constitute Metabolic syndrome (MetS).[6,7] MetS is a group of clinical and biochemical abnormalities that confer a greater risk factor for type-2 DM and CVD.[18] The risk is associated with concomitant hypertension and dyslipidemia, is an additional sum of the individual risk factors,[9,10] Some of the studies found that the treatment of dyslipidemia has favorable effects on both coronary and cerebrovascular events, than to independent decrease the blood pressure benefit.[11,12] Therefore, Dyslipidemia

and hypertension can serve as an easy clinical approach to know persons at greater risk for the and timely interference directed to decrease CVD events[13,19,20] From an epidemiological perspective, a number of cohort studies have strongly indicated a causal relationship between dyslipidemia and risk of future development of hypertension[13,14,15,16,17,18,19,20] However, with a single exception[18] all of these studies have been conducted in non-Asian populations. Therefore, to accumulate further evidence in Asian population, this study was designed to examine whether risk of hypertension is increased in individuals with dyslipidemia in working-age Indian men.

MATERIAL AND METHOD

The present study was a hospital based prospective study conducted in the department of General Medicine, Dr RML Institute of Medical Sciences, Lucknow, India-226010.

The patients were in the range of 35-75 years age group. Both known hypertensive patients who were on treatment for a varying period of time and newly diagnosed hypertensive patients were included in the study. The data collection for the study was from June 2017 to June2019 i.e. for a period of 2 years A total of 200 patients who fulfilled the inclusion criteria were included in the study. A total of 100 non hypertensive controls were included in the study. The hypertensive and healthy controls were selected in to the study by systematic random sampling.

Inclusion Criteria

Patients with essential hypertension with or without complication of hypertension and on medication were included for study.

Systolic blood pressure > 140 mmHg and diastolic >90 mmHg based on average of two readings or one in case of known hypertensive and on anti hypertensive medication, recorded by standard mercury sphygmomanometer, with appropriate cuff size and patient in supine position after 5 minutes of relaxation.

Exclusion Criteria

- Secondary hypertensive subjects were excluded from the study.
- Patients with acute illness like high grade fever and first two weeks following surgery were excluded fromthe study. Purpose of elimination was to obtain a pure picture of relationship between hypertension and serum lipids.
- Patients with diabetes mellitus, hypothyroidism and those receiving lipid-altering drugs were excluded.

Study procedure

After selection of cases, Clinical data wasgathered as per Case Report Form (CRF) which included socio demographic history and details of detailed present, past, family clinical history and drug history. General physical examination including Height, Weight, BMI, Waist Hip ratio was measured. Systemic examination of Cardiovascular, Respiratory, Central Nervous , Renal System and Eye fundoscopy was done. The blood samples were drawn from all the patients after 12 hours of fasting. The patients were asked to have a light fat free diet on the day prior to the sampling. The venepuncture was done in the cubital fossa and about 10 ml of blood was drawn using perfectly dry and sterile syringe and blood was transferred to vaccutainer and within 2 hours of collection, serum was separated by centrifugation .The serum samples were analyzed on the same day. The following investigations were performed

- Complete blood count
- Complete urine examination
- 12 lead ECG
- Xray chest PA
- Fasting lipid profile-Total cholesterol, HDL, LDL, VLDL, Triglycerides.
- Fasting plasma glucose, 2 hour PPBS
- Eye fundoscopy
- 2D ECHO, cardiac isoenzymes, chest x ray were done in relevant cases.
- CT / MRI Brain in relevant cases.

Statistical Analysis

Descriptive analysis of demographic and relevantclinical parameters was done. Various serum lipid levels were considered as primary outcome variables. Categorical variables were presentedas frequencies and percentages. Quantitative variables were presented as mean and standard deviation. The lipid levels were compared between the hypertensive patients and the controls by unpaired t-test. The lipid levels were also compared among hypertensive patients, with or without IHD and CVA. The association between the categorical explanatory and outcome variables was done by cross tabulation and calculating the corresponding odds ratio and 95% CI. Chi square test was used to assess the statistical significance of the association. P value < 0.05 was considered as statistically significant. IBM SPSS version 21 was used for statisticalanalys.

RESULTS

Overall, the mean age of the study population was 38±9 years. Baseline characteristics in the entire population and for the quintiles of serum TC level are presented in Table-1. All variables, except for prevalence of medication for diabetes, current smoking, and regular exercise, were significantly different among the quintiles of TC.

Table 1: Baseline Characteristics of the Study Population, Overall and According to the Quintile of Serum TC Levels.

Variables	Overall (n=3554)	Quintile of TC					*P* Value[a]
		First (n=722)	Second (n=716)	Third (n=708)	Fourth (n=720)	Fifth (n=689)	
TC range, mg/dL	76 to 369	76 to 167	168 to 185	186 to 201	202 to 221	222 to 369	
Age, y	38±9	34±8	37±9	39±9	41±8	42±8	<0.001
Body mass index, kg/m^2	22.7±2.9	21.6±2.6	22.3±2.8	22.6±2.8	23.2±2.8	23.6±2.9	<0.001
Obesity, n (%)	638 (17.9)	64 (8.9)	104 (14.5)	(17.3)	122(22.2)	188 (27.3)	<0.001
Systolic BP, mm Hg	118±11	113±11	115±11	115±11	117±11	118±11	<0.001
Diastolic BP, mm Hg	70±9	67±8	69±9	70±9	71±9	73±9	<0.001
Optimal BP, n (%)	2157 (60.7)	525 (72.7)	451 (63.0)	437 (61.8)	401 (55.8)	341(49.6)	<0.001
Normal BP, n (%)	3375 (23.7)	548 (19.0)	668 (23.3)	670 (23.7)	739 (25.7)	750 (27.2)	
High-normal BP, n (%)	844 (15.6)	60 (8.3)	98 (13.6)	104 (14.5)	134(18.5)	160(23.2)	
TC, mg/dL	195±32	152±12	177±5	193±5	211±6	242±18	<0.001
TG[b], mg/dL	82 (58, 121)	61 (46, 83)	72 (54, 99)	84 (61, 117)	94 (68, 133)	115 (82, 165)	<0.001
LDLC[c], mg/dL	114±29	80±14	99±12	112±13	127±14	153±21	<0.001
HDLC, mg/dL	62±16	58±11	61±13	62±14	62±15	62±16	<0.001
Non-HDLC, mg/dL	134±34	95±15	116±14	132±15	149±16	180±25	<0.001
Fasting plasma glucose, mg/dL	92±14	87±8	89±8	90±10	91±11	92±14	<0.001
HbA1c, %	5.3±0.5	5.2±0.3	5.2±0.4	5.3±0.4	5.3±0.4	5.4±0.5	<0.001
Medication for diabetes, n (%)	13 (0.4)	1(0.3)	3 (0.3)	3 (0.4)	3(0.2)	3 (0.6)	0.16
Impaired fasting glucose/diabetes, n (%)	25 (2.8)	2 (1.4)	3 (1.6)	7(2.8)	6 (3.4)	7 (4.8)	<0.001
Current smoker, n (%)	1078 (30.3)	222 (30.9)	217(30.4)	410 (28.9)	211 (29.4)	222 (32.2)	0.064
Excess alcohol intake, n (%)	581 (16.3)	90(12.5)	110 (15.4)	119 (16.8)	128(17.7)	134 (19.4)	<0.001
Regular exercise, n (%)	833 (23.5)	164 (22.8)	175(24.5)	160 (22.5)	172 (23.9)	162 (23.6)	0.40
Parental history of hypertension, n (%)	760 (21.4)	132 (18.3)	143 (19.9)	156 (22.0)	168 (23.4)	160 (23.3)	<0.001

BP indicates blood pressure; HbA1c, glycated hemoglobin; HDLC indicates high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

[a]ANOVA or chi-square test, as appropriate, among the quintile of serum TC levels.

[b]Median (interquartile range).

[c]Calculated using Friedewald's formula in 14 102 subjects with the TG level <400 mg/dL.

Figure 1 shows the Kaplan–Meier curve for the cumulative hypertension-free survival rate during the follow-up period by quintile for each lipid parameter. Subjects in the highest quintile of all lipid parameters, except HDLC, had the lowest cumulative hypertension-free survival rate. On the other hand, subjects in the lowest quintile of HDLC had the lowest cumulative hypertension-free survival rate.

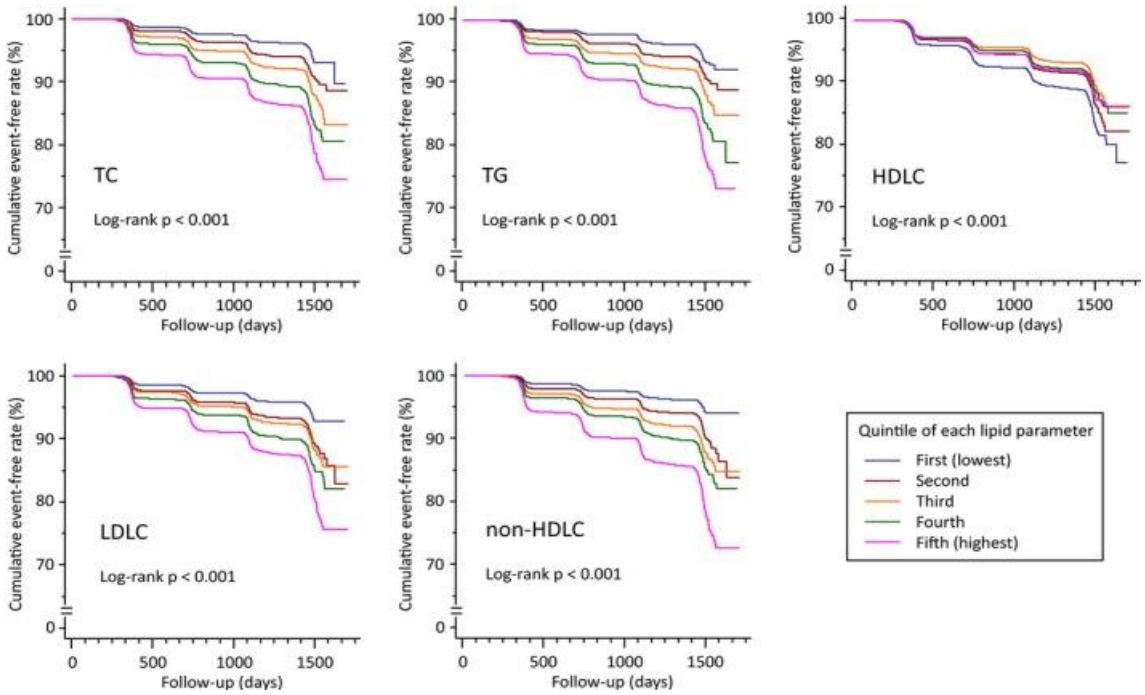

Figure 1: Kaplan-Meier curve for cumulative hypertension-free survival rate by quintile for each lipid parameter. HDLC indicates high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Table 2 shows the HRs for developing hypertension associated with each lipid parameter. In the age-adjusted model, compared to subjects in the lowest quintiles, those with higher TC, TG, LDLC, and non-HDLC levels showed a significantly increased risk of hypertension. For HDLC, higher serum levels were associated with a significantly reduced risk of hypertension. In the multiadjusted model, subjects with TC levels in the highest quintile had a significantly higher HR (1.28; 95% CI: 1.06–1.56) compared to those in the lowest quintile. Similar results were observed for subjects in the highest quintiles of LDLC (HR, 1.27; 95% CI: 1.05–1.53) and non-HDLC (HR, 1.33; 95% CI: 1.09–1.63). Subjects in the fourth quintile of TG had a significantly higher HR compared to those in the lowest quintile, but those in the highest quintile did not. Intriguingly, the HR for subjects in the third quintile of HDLC was significantly lower than those in the lowest quintile, but the HR for subjects in the highest quintile appeared to be higher than both groups, suggesting a U-shaped relationship. The results of the sensitivity analyses after excluding subjects who developed hypertension by the first annual follow-up are presented in Table 3. The results were similar to those obtained in the overall analyses.

Table 2: Association Between Quintile of Each Lipid Parameter and the Risk of Developing Hypertension.

Lipid Parameters and Models	Quintile of Each Lipid Parameter					*P* Value for Trend
	Lowest	Second	Third	Fourth	Highest	
TC, mg/dL	76 to 167	168 to 185	186 to 201	202 to 221	222 to 369	
No. of cases/at risk	35/722	54/716	70/708	96/2879	119/688	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.29 (1.04–1.60)	1.52 (1.24–1.87)	1.87 (1.53–2.28)	2.20 (1.81–2.68)	<0.001
Multiadjusted[a] HR (95% CI)	1.00 (Reference)	1.00 (0.81–1.24)	1.16 (0.95–1.43)	1.19 (0.97–1.45)	1.28 (1.06–1.56)	0.001
TG, mg/dL	14 to 54	55 to 72	73 to 95	96 to 133	134 to 1321	
No. of cases/at risk	36/729	50/694	69/731	92/691	124/708	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.36 (1.10–1.69)	1.62 (1.32–1.98)	2.15 (1.77–2.62)	2.72 (2.25–3.28)	<0.001
Multiadjusted[a] HR (95% CI)	1.00 (Reference)	1.08 (0.87–1.34)	1.17 (0.96–1.44)	1.25 (1.03–1.53)	1.22 (0.99–1.49)	0.027
HDLC, mg/dL	23 to 49	50 to 56	57 to 63	64 to 72	73 to 162	
No. of cases/at risk	103/765	78/722	62/721	63/678	66/668	
Age-adjusted HR (95% CI)	1.00 (Reference)	0.84 (0.73–0.98)	0.67 (0.57–0.78)	0.74 (0.63–0.86)	0.74 (0.63–0.86)	<0.001
Multiadjusted[a] HR	1.00	0.99	0.82	0.99	1.10	0.52

(95% CI)	(Reference)	(0.85–1.15)	(0.70–0.97)	(0.84–1.17)	(0.92–1.30)	
LDLC[b], mg/dL	20 to 89	90 to 105	106 to 119	120 to 137	138 to 301	
No. of cases/at risk	38/713	64/738	64/672	85/699	111/710	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.43 (1.17–1.75)	1.35 (1.10–1.65)	1.63 (1.34–1.97)	1.97 (1.63–2.38)	<0.001
Multiadjusted[a] HR (95% CI)	1.00 (Reference)	1.17 (0.96–1.44)	1.06 (0.86–1.30)	1.16 (0.95–1.41)	1.27 (1.05–1.53)	0.022
Non-HDLC, mg/dL	25 to 105	106 to 123	124 to 140	141 to 162	163 to 334	
No. of cases/at risk	34/739	54/713	70/2738	359/685	124/687	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.42 (1.15–1.77)	1.65 (1.34–2.03)	1.84 (1.50–2.25)	2.56 (2.11–3.11)	<0.001
Multiadjusted[a] HR (95% CI)	1.00 (Reference)	1.23 (0.99–1.52)	1.18 (0.96–1.46)	1.17 (0.96–1.44)	1.33 (1.09–1.63)	0.018

HDLC indicates high-density lipoprotein cholesterol; HR, hazard ratio; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

aAdjusted for age, body mass index, baseline blood pressure category, impaired fasting glucose/diabetes, excessive alcohol intake, current smoking, regular exercise, and parental history of hypertension.

bCalculated using Friedewald's formula in 14 102 subjects with the TG level <400 mg/dL.

Table 3: Association Between Quintile of Each Lipid Parameter and the Risk of Developing Hypertension After Excluding Subjects Who Developed Hypertension by the First Annual Follow-up.

Lipid Parameters and Models	Quintile of Each Lipid Parameter					*P* Value for Trend
	Lowest	Second	Third	Fourth	Highest	
TC, mg/dL	76 to 167	168 to 185	186 to 201	202 to 220	221 to 369	
No. of cases/at risk	76/713	40/702	50/688	65/664	80/678	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.32 (1.03–1.69)	1.51 (1.19–1.92)	1.85 (1.47–2.33)	2.04 (1.63–2.57)	<0.001
Multiadjusted[a] HR (95% CI)	1.00 (Reference)	1.03 (0.80–1.32)	1.17 (0.92–1.49)	1.19 (0.94–1.51)	1.24 (0.82–1.55)	0.025
TG, mg/dL	14 to 54	55 to 72	73 to 94	95 to 132	133 to 1321	
No. of cases/at risk	25/718	37/681	46/686	66/678	88/682	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.48 (1.15–1.92)	1.63 (1.28–2.09)	2.24 (1.77–2.83)	2.85 (2.28–3.57)	<0.001
Multiadjusted[a] HR (95% CI)	1.00 (Reference)	1.20 (0.93–1.55)	1.20 (0.94–1.54)	1.35 (1.06–1.71)	1.32 (1.04–1.68)	0.021
HDLC, mg/dL	23 to 49	50 to 56	57 to 63	64 to 72	73 to 162	
No. of cases/at risk	73/735	55/700	42/701	45/659	18/649	
Age-adjusted HR (95% CI)	1.00 (Reference)	0.84 (0.71–1.00)	0.62 (0.52–0.76)	0.74 (0.61–0.89)	0.73 (0.61–0.88)	<0.001
Multiadjusted[a] HR (95% CI)	1.00 (Reference)	0.99 (0.83–1.18)	0.77 (0.63–0.93)	0.98 (0.83–1.18)	1.10 (0.90–1.35)	0.66
LDLC[b], mg/dL	20 to 89	90 to 104	105 to 119	120 to 137	138 to 301	
No. of cases/at risk	28/703	42/676	50/700	60/673	76/668	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.41 (1.11–1.79)	1.41 (1.12–1.78)	1.61 (1.28–2.02)	1.91 (1.53–2.38)	<0.001
Multiadjusted[a] HR (95% CI)	1.00 (Reference)	1.16 (0.91–1.48)	1.12 (0.89–1.42)	1.17 (0.93–1.47)	1.26 (1.004–1.58)	0.068
Non-HDLC, mg/dL	25 to 104	105 to 122	123 to 140	141 to 161	162 to 334	
No. of cases/at risk	81/696	40/692	53/705	62/678	86/675	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.59 (1.22–2.07)	1.82 (1.41–2.35)	2.04 (1.59–2.62)	2.66 (2.09–3.40)	<0.001
Multiadjusted[a] HR (95% CI)	1.00 (Reference)	1.34 (1.02–1.74)	1.30 (1.01–1.68)	1.30 (1.01–1.68)	1.40 (1.09–1.80)	0.046

HDLC indicates high-density lipoprotein cholesterol; HR, hazard ratio; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

[a]Adjusted for age, body mass index, baseline blood pressure category, impaired fasting glucose/diabetes, excessive alcohol intake, current smoking, regular exercise, and parental history of hypertension.

[b]Calculated using Friedewald's formula in 13 677 subjects with the TG level <400 mg/dL.

Table 4 shows the age- and multiadjusted HRs for developing hypertension when subjects were dichotomized according to the clinical cut-off point for each lipid parameter. In the age-adjusted model, all of the lipid parameters were associated with a significantly increased risk of hypertension. In the multiadjusted model, high TC, high LDLC, and high non-HDLC increased the risk of hypertension with an HR (95% CI) of 1.16 (1.04–1.30), 1.13 (1.01–1.27), and 1.20 (1.06–1.35), respectively.

Table 4: Association Between Clinical Cut-off Point of Each Lipid Parameter and Risk of Developing Hypertension in the Overall Study Population.

Lipid Parameters	Age-Adjusted HR (95% CI)	Multiadjusted[a] HR (95% CI)
High TC (≥220 mg/dL)	1.49 (1.34–1.66)	1.16 (1.04–1.30)
High TG (≥150 mg/dL)	1.77 (1.57–1.98)	1.11 (0.98–1.25)
Low HDLC (<40 mg/dL)	1.30 (1.03–1.65)	1.01 (0.80–1.29)
High LDLC (≥140 mg/dL)	1.40 (1.25–1.57)	1.13 (1.01–1.27)
High non-HDLC (≥170 mg/dL)	1.70 (1.52–1.92)	1.20 (1.06–1.35)

Open in a separate window

HDLC indicates high-density lipoprotein cholesterol; HR, hazard ratio; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

[a]Adjusted for age, body mass index, baseline blood pressure category, impaired fasting glucose/diabetes, excessive alcohol intake, current smoking, regular exercise, and parental history of hypertension.

Results of the subgroup analysis are shown in Table-5. High TC, high LDLC, and high non-HDLC levels were generally associated with an increased risk of hypertension in subjects age <40 years, those with systolic BP ≥120 mm Hg, those without impaired fasting glucose/diabetes, and those with obesity. In contrast, when subjects were stratified by diastolic BP, the association of high TC, high LDLC, and high non-HDLC levels with hypertension was not consistent. Low HDLC levels were only associated with an increased risk of hypertension in subjects with impaired fasting glucose/diabetes. High TG was not associated with a significant risk of hypertension in any of the subgroup analyses.

Table 5: Association Between Clinical Cut-off Point of Each Lipid Parameter and the Risk of Developing Hypertension, Stratified by Age, Systolic BP, Diastolic BP, IFG/DM, or Obesity.

	High TC		High TG		Low HDLC		High LDLC		High non-HDLC	
	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI
Age, y										
<40	1.36	1.08 to 1.71	1.13	0.87 to 1.45	0.84	0.53 to 1.35	1.30	1.02 to 1.66	1.38	1.08 to 1.77
≥40	1.09	0.96 to 1.23	1.09	0.95 to 1.25	1.05	0.79 to 1.39	1.07	0.93 to 1.22	1.13	0.99 to 1.30
Systolic BP, mm Hg										
<120	1.10	0.85 to 1.44	1.23	0.92 to 1.65	0.68	0.36 to 1.29	1.10	0.83 to 1.46	1.17	0.87 to 1.56
≥120	1.17	1.04 to 1.32	1.08	0.95 to 1.24	1.09	0.84 to 1.41	1.14	1.001 to 1.29	1.20	1.06 to 1.37
Diastolic BP, mm Hg										
<80	1.20	1.01 to 1.44	1.20	0.98 to 1.46	0.85	0.55 to 1.30	1.19	0.99 to 1.44	1.15	0.94 to 1.40
≥80	1.10	0.96 to 1.27	1.03	0.89 to 1.20	1.05	0.78 to 1.40	1.08	0.93 to 1.25	1.20	1.04 to 1.39
IFG/DM[b]										
No	1.18	1.05 to 1.32	1.07	0.94 to 1.21	0.87	0.66 to 1.13	1.17	1.04 to 1.32	1.20	1.07 to 1.36
Yes	1.02	0.67 to 1.54	1.45	0.97 to 2.18	2.64	1.44 to 4.84	0.76	0.48 to 1.20	1.14	0.75 to 1.74
Obesity[c]										
No	1.10	0.95 to 1.27	1.13	0.96 to 1.33	1.01	0.67 to 1.52	1.09	0.93 to 1.27	1.10	0.93 to 1.29
Yes	1.24	1.04 to 1.47	1.08	0.91 to 1.29	0.99	0.74 to 1.34	1.18	0.99 to 1.41	1.32	1.11 to 1.57

BP indicates blood pressure; HbA1c, glycated hemoglobin; HDLC, high-density lipoprotein cholesterol; HR, hazard ratio; IFG/DM, impaired fasting glucose/diabetes; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

[a]Adjusted for age, body mass index, baseline BP category, IFG/DM, excessive alcohol intake, current smoking, regular exercise, and parental history of hypertension.

[b]Defined as fasting plasma glucose ≥110 mg/dL, HbA1c ≥6.5%, or current use of glucose-lowering medication.

[c]Defined as body mass index ≥25.0 kg/m2.

DISCUSSION

In this study, it was found that subjects in the highest quintiles of TC, LDLC, and non-HDLC significantly increased the risk of developing hypertension in working-age Indian men. These significant associations were retained when clinical cut-off points were used for the diagnosis of high TC, high LDLC, and high non-HDLC. All of the previous studies that have reported a longitudinal association between lipid parameters and the risk of developing hypertension were conducted in both Non Asian Asian populations[13,14,15,16,17,18,19,20] Therefore, our study provides important evidence that dyslipidemia is significantly associated with an increased risk of developing hypertension in an Asian population.

There could be several pathophysiological mechanisms involved in the association between dyslipidemia and increased risk of hypertension. First, dyslipidemia may impair endothelial function[10,11,21,22,23,24,25] which may consequently disrupt production of nitric oxide and regulation of BP. Second, dyslipidemia may predispose individuals to development of hypertension by reducing baroreflex sensitivity[26] The baroreflex is the regulation of BP by a negative feedback loop; baroreceptors, located in blood vessels, activate the parasympathetic nervous system, which counteracts any changes in BP. Third, dyslipidemia decreases the distensibility of large elastic arteries.[12] This decrease may reduce the windkessel effect[28] which, in turn, increases BP, in particular, systolic BP. Last, physical inactivity and a high-fat diet promote obesity and dyslipidemia. In obese individuals, adipose tissue excessively secretes adipocytokines, such as leptin, thereby inducing insulin resistance and subsequent activation of the sympathetic nervous system and the renin-angiotensin system[9] These biological changes may, in turn, raise BP. In the present study, the multivariate analyses were adjusted for several potential confounding factors, including BMI. However, other adiposity-related residual confounders may be involved in the association between dyslipidemia and risk of hypertension.

Our findings of an association between low HDLC levels and an increased risk of hypertension are consistent with previous reports.[14,16,18,19,20] The main function of HDL is to promote reverse cholesterol transport from macrophages. A cross-sectional clinical study demonstrated an inverse relationship between the cholesterol efflux capacity of HDL, evaluated by the function of ATP-binding cassette transporters, and the intima-media thickness of the carotid artery and prevalence of coronary artery disease. The Dallas Heart Study showed that a higher cholesterol efflux capacity of HDL predicts a lower risk of cardiovascular disease. These results suggest that dysfunctional HDL loses its antiatherogenic action. Rather, an in vivo and in vitro study indicated that dysfunctional HDL is proatherogenic Heritable cholesteryl ester transfer protein (CETP) deficiency is often reported in Japanese people with increased circulating HDLC levels. CETP deficiency may account for ≈27% and 32% of subjects with HDLC ≥60 and ≥80 mg/dL, respectively.[32] In our study, the minimum HDLC level in the highest quintile was 73 mg/dL, suggesting that a certain proportion of the subjects in this group may have had CETP deficiency. Importantly, although it remains a matter of debate, the function of HDL is reportedly impaired in subjects with CETP deficiency. These findings are supported by the results of the Framingham Heart Study, which showed circulating CETP activity to be inversely associated with risk of incident cardiovascular disease. Taken together, we speculate that a certain number of subjects with high HDLC levels in our study had dysfunctional, proatherogenic HDL, which impairs functional and structural arterial properties and thus increases risk of hypertension.

From a clinical perspective, our findings suggest that the association between dyslipidemia and risk of cardiovascular disease may be partly explained by a gradual increase in BP over time. Therefore, health care providers should be attentive to the trajectory of BP, and professional support should be provided to prevent or delay the development of hypertension in patients with dyslipidemia.

This study has several potential limitations. First, our study population included only working-age Japanese men. Therefore, it is unknown whether our results can be extrapolated to women, the elderly, or other ethnic groups. Second, the follow-up duration in our study (median of 4 years) was short compared to previous studies (5–10 years or more)[13,14,15,16,17,18,19,20] Some of the equivocal findings in this study, such as the association between TG levels and risk of hypertension, may be attributable to this limitation. Third, because this was an observational study, the possibility of a reverse association between dyslipidemia and hypertension could not be ruled out. However, in the sensitivity analysis excluding subjects who developed hypertension by the first annual follow-up, the association between dyslipidemia and risk of developing hypertension remained significant. This would reduce the possibility of the reverse association. Fourth, although the duration of exposure for dyslipidemia, as well as other risk factors, may be associated with the risk of developing hypertension, these data were not available in this study. Finally, the serum lipid levels were measured on a single day. Therefore, the intraindividual variation of lipid profiles was not taken into consideration in this study.

In conclusion, our findings show that elevated serum TC, LDLC, and non-HDLC levels were associated with an increased risk of hypertension in working-age Indian men. Overall, our results may contribute to the accumulation of evidence that dyslipidemia increases risk of hypertension in Asian populations. From a clinical perspective, the importance of strict BP management in patients with dyslipidemia was indicated.

Clinical trials that examine whether treatment of dyslipidemia reduces the risk of developing hypertension are needed to verify the results of this observational study.

Funding: None.

Conflict of interest: None.

Ethical clearance: Taken from ethical committee of Institute.

REFERENCE

1. Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, Nakaya N, Nishimoto S, Muranaka M, Yamamoto A, Mizuno K, Ohashi Y. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA study): a prospective randomised controlled trial. *Lancet*, 2006; 368: 1155–1163.
2. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*, 2007; 369: 1090–1098.
3. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*., 1995; 333: 1301–1307.
4. Kario K, Saito I, Kushiro T, Teramukai S, Ishikawa Y, Mori Y, Kobayashi F, Shimada K. Home blood pressure and cardiovascular outcomes in patients during antihypertensive therapy: primary results of HONEST, a large-scale prospective, real-world observational study. *Hypertension*, 2014; 64: 989–996.
5. Ebrahim S, Sung J, Song YM, Ferrer RL, Lawlor DA, Davey Smith G. Serum cholesterol, haemorrhagic stroke, ischaemic stroke, and myocardial infarction: Korean national health system prospective cohort study. *BMJ*., 2006; 333: 352.
6. Elias 6.PK, Elias MF, D'Agostino RB, Sullivan LM, Wolf PA. Serum cholesterol and cognitive performance in the Framingham Heart Study. *Psychosom Med*., 2005; 67: 24–30.
7. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA*., 2008; 300: 2142–2152.
8. Okamura T, Tanaka H, Miyamatsu N, Hayakawa T, Kadowaki T, Kita Y, Nakamura Y, Okayama A, Ueshima H. The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. *Atherosclerosis*, 2007; 190: 216–223.
9. McGill JB, Haffner S, Rees TJ, Sowers JR, Tershakovec AM, Weber M. Progress and controversies: treating obesity and insulin resistance in the context of hypertension. *J Clin Hypertens (Greenwich)*, 2009; 11: 36–41.
10. Casino 10.PR, Kilcoyne CM, Quyyumi AA, Hoeg JM, Panza JA. The role of nitric oxide in endothelium-dependent vasodilation of hypercholesterolemic patients. *Circulation*, 993; 88: 2541–2547.
11. Creager MA, Cooke JP, Mendelsohn ME, Gallagher SJ, Coleman SM, Loscalzo J, Dzau VJ. Impaired vasodilation of forearm resistance vessels in hypercholesterolemic humans. *J Clin Invest*, 1990; 86: 228–234.
12. Wilkinson 12.IB, Prasad K, Hall IR, Thomas A, MacCallum H, Webb DJ, Frenneaux MP, Cockcroft JR. Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia. *J Am Coll Cardiol*, 2002; 39: 1005–1011.
13. Borghi C, Veronesi M, Bacchelli S, Esposti DD, Cosentino E, Ambrosioni E. Serum cholesterol levels, blood pressure response to stress and incidence of stable hypertension in young subjects with high normal blood pressure. *J Hypertens*, 2004; 22: 265–272.
14. Guo ZR, Hu XS, Wu M, Zhou MH, Zhou ZY. A prospective study on the association between dyslipidemia and hypertension. *Zhonghua Liu Xing Bing Xue Za Zhi*, 2009; 30: 554–558. (Chinese with English Abstract).
15. Haffner SM, Miettinen H, Gaskill SP, Stern MP. Metabolic precursors of hypertension. The San Antonio Heart Study. *Arch Intern Med.*, 1996; 156: 1994–2001.
16. 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. M
17. 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: 2561–2568.
18. Sesso 18.HD, Buring JE, Chown MJ, Ridker PM, Gaziano JM. A prospective study of plasma lipid levels and hypertension in women. *Arch Intern Med*., 2005; 165: 2420–2427.
19. Tohidi M, Hatami M, Hadaegh F, Azizi F. Triglycerides and triglycerides to high-density lipoprotein cholesterol ratio are strong predictors of incident hypertension in Middle Eastern women. *J Hum Hypertens*, 2012; 26: 525–532. [PubMed] [Google Scholar]
20. Wildman RP, Sutton-Tyrrell K, Newman AB, Bostom A, Brockwell S, Kuller LH. Lipoprotein levels are associated with incident hypertension in older adults. *J Am Geriatr Soc*., 2004; 52: 916–921.

21. Nagano M, Yamashita S, Hirano K, Takano M, Maruyama T, Ishihara M, Sagehashi Y, Kujiraoka T, Tanaka K, Hattori H, Sakai N, Nakajima N, Egashira T, Matsuzawa Y. Molecular mechanisms of cholesteryl ester transfer protein deficiency in Japanese. *J Atheroscler Thromb*, 2004; 11: 110–121.
22. Joshi 22.Islam S, Pais P, Reddy S, Dorairaj P, Kazmi K, et al. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. JAMA, 2007; 297: 286-94.
23. Genest JG Jr. Dyslipidemia and coronary artery disease. Can J Cardiol., 2000; 16A: 3A-4.
24. Carr M.C., Brunzell J.D. Abdominal obesity and dyslipidemia in the metabolic syndrome: importance of type diabetes and familial combined hyperlipidemia in coronary artery disease risk. J Clin Endocrinol Metab., 2004; 89(6): 2601–2607.
25. H1 Yanai, Tomono Y., Ito K. Th e underlying mechanisms for development of hypertension in the metabolic syndrome. Nutr J., 2008; 7: 10.
26. Zimmet P., McCarty D., de Courten M. The global epidemiology of non-insulin- dependent diabetes mellitus and the metabolic syndrome. J Diabetes Complications, 1997; 11(2): 60–68.
27. Stamler J, Wentworth D, Neaton D. Prevalence and prognostic significance of hypercholesterolemia in men with hypertension: Prospective data on the primary screenees of the Multiple Risk Factor Intervention Trial. Am J Med., 1986; 80: 33–49.