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ORIGINAL ARTICLE

Effects of Remnant Lipoprotein Cholesterol associated with Nitric Oxide in Diabetic and Non-Diabetic Subjects: An Risk Predictor for Future Coronary Heart Disease

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Abstract

Coronary heart disease (CHD) is a multifactorial disease playing a crucial role in genetic and environmental aspects. The early incidence that leads to atherosclerosis is the arterial wall injury through several mechanisms leading to endothelial dysfunction. The mechanisms involved include infection, free radicals, toxins, and physical stresses occur with high blood pressure and blood lipid levels. Remnant lipoproteins, called β-very-low-density lipoprotein, contain triglyceride and cholesterol-rich constituents. Chylomicron remnants enter the arterial wall and get engaged in the sub-endothelial space. After the wall injury, remnant lipoprotein particles bigger than low-density lipoprotein LDL enter the vascular wall and cause atherosclerosis. Nitric oxide (NO) biosynthesis also causes endothelial dysfunction. This study aims to assess the role of remnant lipoprotein cholesterol (RLP-C) and NO in diabetic and non-diabetic subjects who develop CHD. This cross-sectional study was conducted in SRM Medical College Hospital and Research center on 291 subjects appearing the Department of cardiology, Medicine and master health check-up. In that, 97 CHD subjects without diabetes, CHD subject with diabetes, and healthy control patient each, respectively in age group of 25 to 55 years and were age and sex matched. Fasting body fluid samples were collected for lipid profile analysis, and NO was measured by the enzyme-linked immunosorbent assay method. The Student`s t -test and Pearson correlation analysis were used for the statistical analysis. The mean NO levels decreased significantly (12.77 ± 1.37) in CHD subject with Diabetes versus CHD subject without Diabetes (12.97 ± 1.20; P <0.001). RLP-C showed a significant increase (40.25 ± 14.62) in CHD subjects with diabetes when compared to CHD subject without Diabetes (35.65 ± 16.11; P < 0.001). Remnant lipoproteins contribute to form atherosclerotic lesions, and RLP-C predict the risk for CHD. A strong association between NO and RLP-C is associated with the severity in the development of CHD.

Keywords: coronary heart disease; high-density lipoprotein; low-density lipoprotein; nitric oxide; remnant lipoprotein cholesterol

Introduction

Coronary heart disease (CHD) is the most important cause of death and disability in India. It is liable for around one-third or more deaths in individuals above 35 years.[1–3] It has been estimated that half of all middle-aged men and one-third of middle-aged women will show some sign of CHD in the future.[4] Endothelial nitric oxide (NO) plays an essential role in the endothelium structure and vascular tone maintenance. Decreased level of NO causes endothelial dysfunction an early incidence of CHD.[5] Remnant cholesterol is the triglyceride-rich lipoproteins, composed of minimal low-density

lipoproteins (LDL) and intermediate-density lipoproteins in the fasting state and these two lipoproteins together with chylomicron remnants in the nonfasting phase.[6] Remnant lipoproteins (RLPs) are triglyceride-rich atherogenic lipoproteins found in circulation of CHD patient's bloodstream.[7] A high triglyceride level indicates an increased number of circulating triglyceride-rich lipoproteins (TRLs) hydrolyzed into RLPs. These RLPs are rich in cholesterol ester and small nascent TRLs and are therefore thought to be that involved in the progression of atherogenesis.[8] Assessment of RLP-cholesterol (RLP-C) is an advantageous mechanism to evaluate the status of CHD. Recent studies have shown that a higher level of RLP-C deteriorates endothelial cell function in the fasting state.[9] Studies also showed elevated RLP levels in abnormal lipoprotein metabolism, but is also involved in of atherosclerosis progression, CHD, and CHD with dyslipidemia.[10,11] Kugiyama et al.[12] reported that raised RLP in fasting increases the risk for the coronary crisis in patients with CHD RLPs also decrease NO production in the endothelium and thereby inhibit endothelium-dependent relaxation. RLP and LDL are correlated. But unlike LDL, RLP need not undergo oxidation and can be freely adsorbed by macrophage cells which are later converted into foam cells that are the building blocks of arterial plaque. The presence of enhanced RLP levels in survivors of myocardial infarction and individuals with significant CHD is because of this trait of the RLPs. Additionally, RLP also contributes to endothelial dysfunction by damaging the vascular relaxation process and strengthening platelet aggregation.[13] Increased RLP-C and NO levels by endothelial dysfunction are an early marker for atherosclerosis and CHD, respectively.[14] NO is an antiatherogenic particle synthesized by L-arginine through endothelial NO synthase (eNOS) based on cofactors and molecular oxygen that have a short half-life, are the main signaling messenger in cardiac system with vasodilator effect, and are an endothelial relaxing agent.[15,16] Decreased endothelial NO production enhances the risk for CHD.[17] Endothelium NO controls vascular tone, vascular integrity by inhibition of platelet aggregation, leukocyte adhesion, smooth muscle proliferation.[18] Stroke, hypertension, atherosclerosis, and congestive heart failure are caused because of defective NO signaling.[19,20] Massive production of superoxide anion cause diminished NO bioavailability.[21] Emerging experimental and clinical related technological developments over the last three eras found RLP as the investigative target as therapeutics for atherosclerosis causatives.[22]

The early step in atherosclerosis is the damage to the endothelial cell with loss of vascular protective effect of NO.[23] Previous studies report that RLP-C has enhanced association with CHD versus LDL cholesterol (LDL-C). Epidemiological studies demonstrated that elevated LDL-C or diminished high-density lipoprotein (HDL)-C levels of are a self-regulating threat factor for CHD.[24,25] No report to date mentions if increased triglycerides levels are also a self-determining threat factor.[26] Hence, this study evaluated the serum NO, lipid profile, and its relation with RLP-C.

Materials and Methods

Study design and population

This cross-sectional study was conducted from October 2019 to March 2020 on patients attending the Cardiology and medicine outpatient at SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India. The study included 291 subjects who were age and sex-matched and between the age group 25 to 55 years. Ninety-seven patients each of CHD without diabetes, CHD with diabetes, and normal healthy control patients were selected. The control patients were chosen from the master health check-up program and medicine outpatient of the same institute. This study was approved by the institutional ethical committee at SRM Medical College Hospital and Research Centre (ECN: 1513/ICE/2018) and adhered to the Declaration of Helsinki. Written informed consent was collected from all participants at the time of enrolment.

Inclusion criteria

Group 1 (Control patients): no clinical and electrocardiogram evidence of CHD, diabetes mellitus, hypertension, smoking, and family history of CHD.

Group 2 (Non-Diabetic CHD): CHD patients were selected on the basis of coronary angiography, admitted in hospital for first time with chest pain, ECG changes, increased cardiac markers such as creatinine phosphokinase (CPK-MB), and troponin level.

Group 3 (Diabetic CHD): CHD subjects with diabetes.

Baseline measurement

Medical and demographic data were collected at the period of enrolment, and documents were deidentified before investigation. Basic information on age, gender, history of diabetes, hypertension, and the medications used were collected using a questionnaire during the clinical appointment. Questionnaires were evaluated by an expert questioner before entering them into the database. Arterial blood pressure was measured using standard methods in triplicate, and the averaged values were used for the analysis.

Measurement of laboratory parameters

The laboratory report outcomes of all the participants were recorded and their fasting samples were collected aseptically from the antecubital vein. The blood was centrifuged at 2500 rpm for 15 min, and the separated serum was used for the routine lipid profile estimation using direct antibody inhibition. Total cholesterol and triglycerides were estimated by enzymatic end-point cholesterol esterase-peroxidase methods (Beckmann Coulter AU480 Analyzer, Beckmann Coulter Brea, CA).

Measurement of RLP-C

The RLP-C was calculated using Equation (1) already used in a previous study.[27]

RLP-C = Total cholesterol – (HDL-C + LDL-C) (1)

Measurement of Nitric Oxide

Serum NO was measured by using the Griess reagent as nitrite/nitrate in CHD and control patients. Absorbance was measured at 540 nm in UV-Spectrophotometer.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS, Chicago, IL, version 21). The data were shown as mean and standard deviation. $P < 0.05$ was considered significant. Statistical significance for all the groups was analyzed by Student's t-test. Pearson's correlation coefficient was calculated to find out the correlation between different parameters.

Results

Totally 291 subjects were included who were age and sex matched in the age group 25-55 years 97 Non-Diabetic CHD subject (45 males and 46 females) with average age 42.3±10.5 years, 97 Diabetic CHD subject (45 males and 46 females) with average age 40.6±6.4 years and 97 healthy control (40 males and 51 females) with average age of 41.8±9.7. Majority of CHD subjects are in age group of 35-55. While most of the control subjects were fall in the age group of 30-45 years. BMI, Waist Circumference, Waist Hip Ratio, systolic blood pressure were significantly increased ($p<0.05$) in CHD patients compared to controls as depicted in [Table 1]. The study shows FBG, Total cholesterol, Triglyceride, LDL-C, VLDL-C, LDL-C/HDL-C ratio, Total Cholesterol/HDL ratio are significantly elevated in both diabetic and non-diabetic subjects with CHD when compared to control. Among the three groups the mean levels of HDL-C levels did not vary significantly.

The mean level of RLP-C values were significantly increased in both diabetic and non-diabetic subjects with CHD when compared with controls ($P <0.001$). And the mean level of Serum Nitric oxide show a significant decrease in both diabetic and non-diabetic subjects with CHD when compared with controls ($P < 0.001$) [Table 2].

Pearson correlations analysis between RLP-C and conventional biomarker in diabetic and non-diabetic subject with CHD

RLP-C is positively correlated with body mass index (BMI), waist circumference, waist-hip ratio, triglyceride, HDL-C, LDL-C, very-low-density lipoprotein-cholesterol (VLDL-C), TC/HDL-C ratio, and LDL-C/HDL-C ratio. RLP-C was negatively correlated with FBG, HDL-C, and NO in non-diabetic patients.

In diabetic patients, RLP-C is positively correlated with duration of diabetes, BMI, waist circumference, FBG, triglyceride, HDL-C, LDL-C, VLDL-C, TC/HDL ratio, and LDL/HDL ratio. RLP-C was negatively correlated with waist-hip ratio, TC, HDL-C, and NO.

Table1 Demographics and baseline characteristics of CHD and healthy control patients.

Parameters		Control patients (n = 97)	CHD patients without diabetes (n = 97)	CHD patients with diabetes (n = 97)	P value[a]
Mean age (years, mean ± standard deviation)		41.8 ± 9.7	42.3 ± 10.5	40.6 ± 6.4	NS
Sex	Male (%)	40 (41.2 %)	45 (46.3 %)	58 (59.7 %)	–
	Female (%)	57(58.7 %)	52(53.6 %)	39(40.3%)	–
BMI (kg/m^2)		21.91± 0.37	23.47± 0.35	24.03± 0.19	< 0.0001***
WC (cm)		90.9 ± 10.1	93.8 ± 9.6	98.8 ± 4.3	< 0.0001**
Waist to hip ratio		0.94 ± 0.02	1.01 ± 0.01	1.05 ± 0.03	< 0.0001**
Waist to height ratio		0.56 ± 0.01	0.62 ± 0.02	0.65 ± 0.01	< 0.0001***
Systolic blood pressure (mm Hg)		112.73 ±18.32	119.38 ± 16.57	122.26 ± 13.95	< 0.0001**
Diastolic blood pressure (mm Hg)		77.69 ± 7.95	74.58 ± 13.26	70.16 ± 16.47	< 0.0001***
Alcohol drinking	Drinkers	10 (10.3 %)	31 (31.9 %)	37 (38.1 %)	
	Non-drinkers	87 (89.6 %)	66 (68 %)	60 (61.8 %)	–
Diabetes	Diabetic	0	0	97 (100%)	–
	Non-diabetic	97 (100%)	97 (100%)	0	
Family history of CHD	Yes	0	25 (25.7 %)	33 (34 %)	
	No	97 (100%)	72 (74.2 %)	64 (65.9 %)	–

BMI, body mass index; NS, not significant; WC, waist circumference. [a]P < 0.05 was considered significant.
***Very highly significant.
**Highly significant.

Table 2 Comparison of biochemical parameters between CHD subjects and healthy controls.

Parameters	Control patients (n = 97) (Mean ± SD)	CHD patients without diabetes (n = 97) (Mean ± SD)	CHD patients with diabetes (n = 97) (Mean ± SD)	P value[a]
FBG (mg/dl)	95.7 ± 7.68	97.29 ± 6.98	169.98 ± 66.28	< 0.0001**
TC (mg/dl)	169.20 ± 16.13	235.6 ± 34.27	242.73 ± 40.33	< 0.0001***
TG (mg/dl)	82.74 ± 28.41	140.19 ± 60.71	178.86 ± 90.08	< 0.0001**
HDL (mg/dl)	46.96 ± 9.4	37.64 ± 4.12	37.83 ± 4.25	< 0.0001**
LDL (mg/dl)	106.54 ± 12.45	161.31 ± 24.48	164.64 ± 27.32	< 0.0001***
VLDL (mg/dl)	17.26 ± 8.77	28.06 ± 12.14	34.08 ± 14.29	< 0.0001***
TC/HDL ratio	3.71 ± 0.70	6.17 ± 1.14	6.50 ± 1.36	< 0.0001**
LDL/HDL ratio	2.35 ± 0.53	4.22 ± 0.75	4.41 ± 0.90	< 0.0001***
TG/HDL ratio	1.84 ± 0.78	6.17 ± 1.15	6.50 ± 1.36	< 0.0001***
RLP-C (mg/dl)	15.69 ± 12.15	35.65 ± 16.11	40.25 ± 14.62	< 0.0001***
Nitric oxide (µmol/l)	19.08 ± 4.74	12.97 ± 1.20	12.77 ± 1.37	< 0.0001***

FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL , low-density lipoprotein; RLP-C, remnant lipoprotein cholesterol; NS, not significant.
[a]P < 0.05 is significant.
***Very highly significant.
**Highly significant.

Pearson correlations analysis between NO and conventional biomarker in diabetic and non-diabetic subject with CHD

NO was positively correlated with FBG, TC, and HDL-C. It was negatively correlated with BMI, waist circumference, waist-hip ratio, triglyceride, HDL-C, LDL-C, VLDL-C, TC/HDL ratio, LDL/HDL ratio, and RLP-C.

In diabetic subjects, NO was positively correlated with waist circumference and HDL-C. It was negatively correlated with duration of diabetes, BMI, waist-hip ratio, triglyceride, LDL-C, VLDL-C, TC/HDL ratio, LDL/HDL ratio, and RLP-C (Table 3).

Table 3 The Pearson correlations analysis between RLP-C and NO with other biochemical parameters in diabetic and non-diabetic subjects with CHD.

Variables	CHD patients without diabetes				CHD patients with diabetes			
	RLP-C	P value	NO	P value	RLP-C	P value	NO	P value
Duration of diabetes	–	–	–	–	0.009[a]	< 0.0001	–0.061[b]	< 0.0001
Body mass index	0.023[a]	< 0.0001	–0.103[b]	< 0.0001	0.104[a]	< 0.0001	–0.044[b]	< 0.0001
Waist circumference	0.044[a]	< 0.0001	–0.022[b]	< 0.0001	0.035[a]	< 0.0001	0.045[a]	< 0.0001
Waist hip ratio	0.240[a]	< 0.0001	–0.288[b]	< 0.0001	–0.032[b]	< 0.0001	–0.158[b]	< 0.0001
Fasting blood glucose	–0.130[a]	< 0.0001	0.078[a]	< 0.0001	0.047[a]	< 0.0001	–0.216[b]	< 0.0001
Total cholesterol	0.110[a]	< 0.0001	0.031[a]	< 0.0001	–0.050[b]	< 0.0001	–0.024[b]	< 0.0001
Triglyceride	0.065[a]	< 0.0001	–0.143[b]	< 0.0001	0.181[a]	< 0.0001	–0.012[b]	< 0.0001
HDL-C	–0.227[b]	< 0.002	–0.040[b]	< 0.002**	–0.312[b]	< 0.0001	0.090[a]	< 0.002**
LDL-C	0.431 A	< 0.0001	–0.991[b]	< 0.0001	0.226[a]	< 0.0001	–0.999[b]	< 0.0001
VLDL-C	0.064[a]	<0.0001	–0.141[b]	< 0.0001	0.176[a]	< 0.0001	–0.113[b]	< 0.0001
TC/HDL ratio	0.737[a]	< 0.0001	–0.670[b]	< 0.0001	0.746[a]	< 0.0001	–0.651[b]	< 0.0001
LDL/HDL ratio	0.220[a]	< 0.0001	–0.009[b]	< 0.0001	0.165[a]	< 0.0001	–0.291[b]	< 0.0001
Nitric oxide	–0.401[b]	< 0.0001	–	–	–0.223[b]	< 0.0001	–	–
RLP-C	–	–	–0.401[b]	< 0.0001			–0.223[b]	< 0.0001

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RLP-C, remnant lipoprotein cholesterol ; NO, Nitric Oxide.
[A]Positive correlation.
[B]Negative Correlation.

Discussion

All the lipid abnormalities were identified as risk markers for CHD. LDL carrying high cholesterol penetrates the arterial wall and is at high oxidation risk.[28] LDL in the early phase of modification is oxidized in subendothelial space. Here the components of lipid interact with reactive oxygen species and produce several varieties of lipid oxidation products.[29] Sampson et al.[30] reported that even after the LDL-C reduction to its recommended concentration, there is still considerable residual risk of reoccurring cardiovascular events. Although statins lower LDL-C, it only has a minimal effect on triglycerides. An increase in triglycerides concentration also increase the remnant cholesterol. Remnant cholesterol has a double association with ischemic heart disease than LDL-C. A significant positive correlation between LDL-C, triglycerides, and RLP-C in CHD patients was observed in this study. Ghodsi et al.[31] suggested that non-HDL-C is an important robust risk marker for CHD than LDL-C alone. The oxidized LDL and triglyceride-rich lipoprotein undergoes lipolysis and release cholesterol-rich RLP.[32] Components of lipid metabolism such as cholesterol, triglycerides, and lipoproteins are involved in the pathogenesis of atherosclerosis. Lipid metabolism was significantly impaired in diabetes patients with CHD versus non-diabetic patients with CHD.[33] Elevated serum LDL and concentrations of triglyceride are responsible for the formation of atherosclerotic lesions.[34]

The roles of lipid metabolism and LDL modification are essential for the development of atherosclerosis.[35] RLP increases in abnormal lipoprotein metabolism, atherosclerosis progression, and CHD.[36] LDL particles enter the arterial wall and increase its risk for oxidation in subendothelial space in the early phase of modification. The components of lipid are related with ROS and produce several varieties of lipid oxidation products.[37] RLP constituents are derived from VLDLs and chylomicrons, which are the most important transporters of plasma triglycerides. A positive correlation between RLP-C with triglycerides, LDL-C, and VLDL-C was observed in this study.

A previous study showed that the RLP-C could pass the endothelium and formed foam cells after being adsorbed by macrophages. These foamed RLPs might cause dysfunction in endothelial vasomotor and increase the risk for CHD in patients with hypertriglyceridemia.[38] In this study, a negative correlation between RLP-C and NO was recorded.

Hypertriglyceridemia was associated with endothelial dysfunction.[39] Kugiyama et al. [30] stated that RLP levels were associated with abnormal endothelium-dependent vasomotor and proposed that the reduction in the bioactivity of coronary NO may be responsible for the inhibitory effects of RLPs.

NO plays an essentially defensive role during the initial phases of CHD by inhibiting the adhesion of leucocytes.[40] They may play an advantageous role in hemodynamically mediated coronary ischemia by causing coronary vasodilatation. Because the expression and activation of endothelial NO synthase are dynamic to endothelial cell function.[41] This article suggests that RLPs might impair endothelial cell function by altering eNOS. The current study demonstrated that increased levels of RLPs in fasting serum predict the development of clinical coronary actions in patients with CHD independently of other risk factors like NO.

Higher remnant cholesterol levels can be decreased by adopting routine modifications and pharmaco-therapy.[42] Changes in lifestyle, weight reduction, decreased alcohol and saturated fat intake, avoidance of smoking, and physical activity help in lowering remnant cholesterol levels by reducing the hepatic secretion of VLDL particles and enhancing their clearance. Statins, niacin, and fibrates play a pivotal role in decreasing remnant cholesterol levels.[43] RLP-C calculation is not being widely practiced, and not much information is available in the Asian population. Although genetics plays a great role in the levels of RLP, utilization of omega-3 fatty acids can significantly lower their levels. Therapies that usually lower triglycerides are also effective at lowering RLP. Many researchers have to pay attention to RLP as atherogenic particles. RLP not only increases lipoprotein metabolism defect but is also related to the progression of atherosclerosis and CHD.[44] Assessment of RLP-C levels can be included for better risk stratification. Optimal standardization of procedures to estimate RLP-C is desirable. Large-scale studies may help to understand the role of RLP-C in the prediction of cardiovascular events. The utilization of triglycerides is a CHD risk because of the variability of triglyceride-rich lipoproteins particle species like chylomicrons and VLDL.[45,46]

Limitations

This study had some limitations. First, the relatively small sample size limits the study outcomes. Second, the cross-sectional nature of the study demonstrates only the associations with CHD severity. Small sample size and more in-depth work on the role of NO and RLP-C are needed to evaluate the prevention of future risk for CHD.

Conclusion

The elevated level of RLP-C and decreased production of NO play a pivotal role in endothelial dysfunction. These contribute to the progression of CHD leading, to morbidity and mortality.

Author Contributions

All authors have made a critical contribution to the research work reported in this manuscript. KK performed the design and drafting of the study. TJ helped with data collection and data analysis. KN was pivotal in the critical revision of the draft. BK carried out the interpretation work.

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Conflict of Interest

No potential conflict of interest was reported by the authors.

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