

Original Article

Lack of an Association or an Inverse Association Between Cholesterol and Coronary Artery Disease: A Case-Control Study

Sanjaya Kumar Shrestha¹, Nikky Maharjan¹, Siddhartha Kumar Shrestha²

¹Department of Internal Medicine, Patan Academy of Health Sciences, Lalitpur Nepal

²Star Hospital, Lalitpur, Nepal

ABSTRACT

Introduction: Cholesterol has been blamed as the principal cause of cardiovascular diseases, however, it is a common observation that most coronary artery disease patients do not have strikingly high cholesterol values, often falling within the desirable range, and also many patients with high cholesterol levels do not have any atherosclerotic cardiovascular diseases. Therefore, we decided to investigate whether there is an association between cholesterol levels and coronary artery disease.

Materials and Methods: This is a case-control study conducted on a total of 313 coronary heart disease patients and 369 controls diagnosed by coronary angiogram. Fasting lipid profile was analyzed for both cases and controls. The study extended for a period of three years from 2018 July to 2020 June.

Results: Total cholesterol ($p < 0.05$) and Low-Density Lipoprotein ($p < 0.05$) levels were significantly lower among the cases, while triglyceride and High-Density Lipoprotein levels of cases were similar to the controls.

Taking age into consideration, there was no significant difference in the total cholesterol and Low-Density Lipoprotein levels between cases and controls below the age of 60 years, however, above the age of 60 years, total cholesterol and Low-Density Lipoprotein were significantly lower in the cases ($p < 0.05$).

Conclusions: The findings of the present study indicated that either there was no association between cholesterol levels and coronary artery disease or an inverse association when age was taken into consideration, as above 60 years of age the cholesterol level was found to be significantly lower in the patients of coronary artery disease compared to controls.

Keywords: Cholesterol; Coronary artery disease; Lipoproteins; Triglyceride;

Correspondence:

Dr. Sanjaya Kumar Shrestha, MD
Department of Internal medicine, Cardiac Unit
Patan Academy of Health Sciences, Lalitpur Nepal
ORCID ID: 0000-0003-2860-6293
Email: sanjayakumar70@gmail.com

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INTRODUCTION

In the last half a century, high-fat diet and cholesterol have been blamed as the principal causation of cardiovascular diseases (CVD) like coronary heart disease and stroke. The fear of cholesterol has been so deeply rooted in the minds of both medical

and non-medical communities that almost every patient visiting a Cardiology clinic is concerned about their cholesterol numbers. Despite the very wide use of cholesterol-lowering medicines like statins for the last ten to twenty years, for both primary and

secondary prevention of CVDs, it has been the number one killer among non-communicable diseases. World Health Organization (WHO) estimated that 17.9 million people died from CVDs in 2019, representing 32% of all global deaths. Of these deaths, 85% were due to heart attack and stroke.¹

However, it is a common observation that the lipid numbers of most coronary heart disease patients are not strikingly high, rather they fall within the desirable range given by the National Cholesterol Education Program (NCEP) of the United States, the most influential body that determines the normal values of cholesterol. Conversely, it is also quite common to see patients with high cholesterol having perfectly normal coronaries.

According to the cholesterol hypothesis, an elevated blood level of cholesterol is a direct cause of atherosclerosis. Therefore, taking any action to reduce cholesterol levels should be an important step in lowering the risk of developing atherosclerotic CVD. But, why does lowering LDL cholesterol levels with statins improve CV outcomes, while lowering LDL levels with other drugs does not? Niacin, ezetimibe, bile acid sequestrants, fibrates, and CETP inhibitors, which lower cholesterol levels², and low-fat diets³, generally have not been able to show improved CV outcomes. Moreover, despite statin becoming the biggest money-making drug in the history of the pharmaceutical industry, CVDs are on the rise. In 2010, 11.6 % of Americans took them (37 million out of 309 million), and following the 2013 ACC/AHA guidelines, an additional 10.2 million Americans without CVD, became candidates for statin therapy, and in 2014, 13.5% (43 million out of 318 million) Americans were taking statins.⁴ In the last decade or so, most of the studies have been done with the preconceived idea that cholesterol is the principal cause of atherosclerotic disease and the studies have focused primarily on the level of cholesterol numbers in different populations or the prevalence of various established risk factors of atherosclerosis. Only a few studies have compared the lipid numbers of coronary heart disease patients with that of the normal population. We have designed this study to compare the lipid profile of angiographically proven coronary artery disease patients with that of individuals with angiographically proven normal coronaries. To our knowledge, there is no other study done in Nepal that compares lipid profiles of individuals with angiographically proven normal coronaries with angiographically proven coronary artery disease patients.

MATERIALS AND METHODS

The present study is a case-control study conducted on a total of 313 coronary heart disease patients diagnosed by coronary angiogram, and 369 controls who were either clinically diagnosed to be free from coronary heart disease or angiographically proven individuals having normal coronaries in the cath lab of Patan Hospital, a teaching hospital in the Kathmandu valley. All individuals whose angiogram and lipid profile reports were available were included in the study irrespective of their status of smoking, statin intake, and also with or without diabetes and hypertension. Cases and controls ranged from the age of 31 years to 90 years. There were altogether 208 (56.37%) males in the control group and 168 (53.85%) males in the cases (Table 1). Individuals with very high TC of more than 300 mg/dL were excluded from the study because they are presumed to be having familial hypercholesterolemia (FH), a genetic disorder in which there is either deficiency or almost complete lack of functioning

LDL-receptors through which the plasma cholesterol in the form of LDL is incorporated into the cell membrane. The study extended for a period of three years from 2018 July to 2020 June. This study was initiated after taking consent from patients and after prior approval by the Institutional Review Committee of Patan Hospital.

Blood samples of both cases and controls were drawn after an overnight fast for 10-12 hours. The lipid profile was analyzed on the same day of sample collection. Total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels were analyzed. The study was done with purposive sampling. The data in this study were analyzed using SPSS version 15 and an independent t-test. The p-value of <0.05 was taken as significant.

RESULTS

TC and LDL levels were significantly lower among the cases compared to that of the controls, while TG and HDL levels of cases were similar to that of the controls. The mean and standard deviation values of TC in the cases were 167.87 ± 59.36 mg/dl (Mean \pm SD) vs. 193.29 ± 48.68 mg/dl in the controls ($p < 0.001$). LDL level in the cases was 92.46 ± 51.69 mg/dl vs. 115.91 ± 44.67 mg/dl in the controls ($p < 0.001$). TG level in the cases was 167.36 ± 89.76 mg/dl vs. 170.69 ± 96.24 mg/dl in the controls ($p = 0.655$). HDL level in the cases was 42.26 ± 15.42 mg/dl vs. 43.49 ± 10.42 mg/dl in the controls ($p = 0.251$) (Table 2 and fig. 1).

Table 1. Demography of cases and controls

	Control	Case	p-value
Sex (male)	208 (56.37%)	168 (53.85%)	-
Hypertension	239 (53.3%)	209 (46.7%)	0.094
Diabetes mellitus	107 (45.5%)	128 (54.5%)	<0.001
Smoker	122 (47.1%)	137 (52.9%)	<0.001
Statin intake	37 (29.6%)	88 (70.4%)	<0.001

Table 2. Mean and standard deviation values of total cases and controls

	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
Control	193.29 ± 48.68	170.69 ± 96.24	43.49 ± 10.42	115.91 ± 44.67
Case	167.87 ± 59.36	167.36 ± 89.76	42.26 ± 15.42	92.46 ± 51.69
p-value	<0.001	0.655	0.251	<0.001

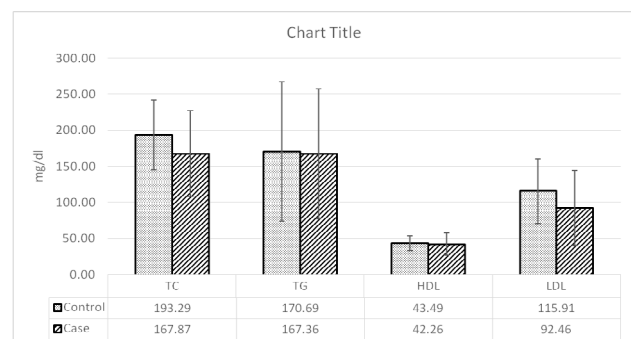


Figure 1. Lipid profile of total cases and controls

Taking age into consideration there was no significant difference in the TC and LDL levels between cases and controls below the age of 60 years. The mean and standard deviation values of TC in the cases were 185.59±78.84 mg/dl vs. 198.47±47.22 mg/dl in the controls (p=0.191). LDL level in the cases was 103.75±71.78 mg/dl vs. 117.91±43.38 mg/dl in the controls (p=0.122) (Table 3 and fig. 2).

Table 3. Mean and standard deviation values in age<60 years (with/without statin)

	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
Control	198.47±47.22	180.64±111.17	43.14±10.25	117.91±43.38
Case	185.59±78.84	190.96±100.59	42.46±14.14	103.75±71.78
p-value	0.191	0.496	0.707	0.122

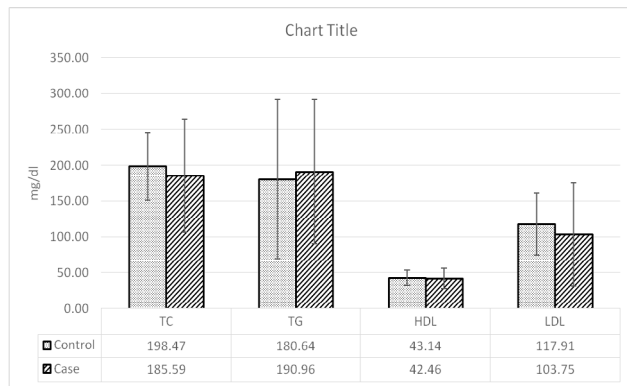


Figure 2. Lipid profile of cases and controls in age <60 years (with/without statin)

However, above the age of 60 years, TC and LDL were significantly lower in the cases compared to the controls. The mean and standard deviation values of TC in the cases were 160.08±52.61 mg/dl vs. 182.05±44.62 mg/dl in the controls (p=0.004). LDL level in the cases was 85.75±45.11mg/dl vs. 110.69±52.09 mg/dl in the controls (p=0.001) (Table 4 and fig. 3).

Table 4. Mean and standard deviation values in age>60 years (with/without statin)

	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
Control	182.05±44.62	157.04±74.87	43.88±9.37	110.69±52.09
Case	160.08±52.61	168.27±92.51	42.47±16.57	85.75±45.11
p-value	0.004	0.388	0.471	0.001

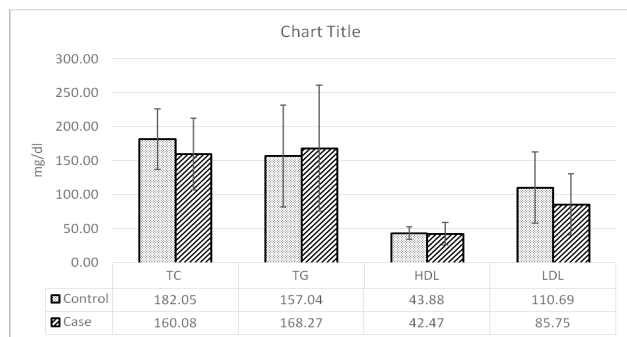


Figure 3. Lipid profile of cases and controls in age >60 years (with/without statin)

DISCUSSION

The present study shows that either there is no significant difference in the cholesterol numbers of the coronary artery disease group and the control group, or there is an inverse association between cholesterol and coronary artery disease. More specifically, there is a lack of an association between serum cholesterol levels and coronary artery disease below the age of 60 years, and there is an inverse association between serum cholesterol levels and coronary artery disease above the age of 60 years. This finding is in accordance with the study published in the British Medical Journal by Uffe Ravnskov, et al in the year 2016.⁵

This finding seems to be contradictory to the mainstream line of thought on the cholesterol hypothesis; however, there has never been any hard proof that cholesterol is the cause of atherosclerosis to date. What is known is that cholesterol is associated with atherosclerotic plaques, but there are many other cells and substances associated with atherosclerotic plaques. The main components of atherosclerotic plaques are fibrous elements such as connective tissue, extracellular matrix, including collagen, proteoglycans, and fibronectin elastic fibers, smooth muscle cells, and inflammatory cells, such as monocyte-derived macrophages and T-lymphocytes, and macrophages containing cholesterol known as foam cells. The role of cholesterol inside foam cells has never been elucidated to date. Whether cholesterol, as a component of the atherosclerotic lesion, has a protective role or harmful role has never been elucidated. Therefore cholesterol is associated with atherosclerotic lesions but the association does not always translate into a cause.

It is a well-known fact that cholesterol is extremely important for the maintenance of the integrity (the proper fluidity and rigidity) of the cell membrane made up of a bilayer of phospholipids. The bilayer of phospholipids is fluid at high temperatures and solid at low temperatures, therefore it is the cholesterol interspersed between the molecules of phospholipids that maintain the proper integrity of the cell membrane. Cholesterol also has many other functions in the cell membrane. There are areas of microdomains in the bilayer of phospholipids known as lipid rafts. These are areas highly rich in cholesterol and sphingolipids. Their extremely important roles in signal transduction and immunologic reactions have been recently understood.⁶ Lipid rafts form the scaffolds for various receptors required for signal transduction. Cholesterol is the principal component of vitamin D and many hormones like androgens, estrogens, progesterone, glucocorticoids, and mineralocorticoids. Cholesterol is required for bile acid synthesis which in turn is required for the absorption of fat and fat-soluble vitamins like A, D, E, and K. Cholesterol is such an important component of a cell that every nucleated cell has the mechanism of synthesizing its cholesterol through a chemical pathway known as Mevalonate pathway, and is also able to incorporate cholesterol circulating in plasma through receptor-mediated endocytosis by Low-Density Lipoprotein Receptors (LDL-R). Cholesterol homeostasis is tightly maintained by a complex network of intracellular organelles, proteins known as Sterol Regulatory Element Binding Proteins (SREBP system), and enzymes that involve cholesterol synthesis, import, export, esterification, and metabolism.⁷ The decrease in ER cholesterol induces the translocation of SREBP from the ER to the Golgi apparatus and then to the nucleus for the transcriptional activation of the target genes, including those involved in cholesterol

uptake and biosynthesis resulting in the upregulation of LDL-R in the cell membrane.⁸ The upregulation of LDL-R in the cell membrane leads to more cholesterol being incorporated into the cell through LDL-C (the exogenous cholesterol that comes in the plasma either through the foodstuffs we ingest or from the liver). Most of the cholesterol either synthesized *de novo* or acquired from plasma through LDL-R is distributed in the cell membrane for its integrity and the formation of lipid rafts. Therefore, it can be argued that how can something so vital for the cell can be the cause of atherosclerotic lesions. Moreover, it has now been understood that the atherosclerotic process is an inflammatory process. Anti-inflammatory therapy targeting the interleukin-1 β innate immunity pathway with canakinumab (human monoclonal antibody) at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent CV events than placebo, independent of lipid-level lowering.⁹ Various experiments have shown that depletion of cholesterol from the cell membrane results in disintegration or damage of the cell membrane.¹⁰ Any sort of damage in our tissue results in an inflammatory reaction, and it is the inflammatory reaction that initiates the atherosclerotic process.^{11,12} The initiator of damage could be chemical, e.g., the end-glycation products in diabetes mellitus that result in endothelial dysfunction, bacterial or viral invasion, or mechanical, e.g., high wall shear stress (WSS) on the vascular endothelium due to high blood pressure or cholesterol depletion of the cell membrane. A study published in *Circulation*¹³ regarding Coronary Artery Wall Shear Stress demonstrated that regions with high WSS developed atherosclerotic plaques, increased calcification, and necrotic core, thinning of the fibro-fatty cap, and vulnerability to rupture. In a study of endothelial cells from baboon aorto-iliac grafts, high-WSS regions were associated with increased expression of substances known to promote vascular inflammation and vascular calcification.¹⁴

This argument also supports the possible reason for early atherosclerosis in homozygous and heterozygous familial hypercholesterolemia. There is either deficiency or an almost complete absence of LDL-Rs in familial hypercholesterolemia.¹⁵ Therefore in these conditions, cells, particularly vascular endothelial cells, which are constantly under mechanical wall shear stress and injury, are not able to acquire adequate exogenous cholesterol from the plasma and this could be the reason for the

vulnerability of vascular endothelial cell membranes resulting in damage and inflammation leading to atherosclerosis.

Even as early as 1936, Lande and Sperry found that people with low TC were just as atherosclerotic as people with high TC.¹⁶ The positive association between TC and degree of atherosclerosis noted in the study by Solberg et al. disappeared when those with TC above 350mg/dL were excluded.¹⁷ Similarly, even in the famous Framingham study, there is a huge overlap of TC values between the individuals with no coronary artery disease and coronary artery disease patients. The only significant difference is seen when the TC levels are above 300mg/dL.¹⁸ We presume that people with TC levels above 300 mg/dL are FH patients and their high plasma level of TC is because of their inability to incorporate plasma cholesterol due to deficiency of LDL-R in heterozygous FH or due to complete absence of LDL-R in homozygous FH on their cell surface, and their early development of atherosclerotic lesions are due to inadequate cholesterol in their bilayer phospholipid membrane required to maintain the integrity of the membrane. Low levels of cholesterol may increase their vulnerability to damage by various mechanical, chemical, or microbial insults progressing to inflammatory reaction and atherosclerosis.

CONCLUSIONS

Though cholesterol has been demonized as the principal cause of cardiovascular diseases in the last half a century, and statins as the greatest liberator of this disease, neither a low cholesterol diet nor the extensive use of statins have been able to show a decreasing trend of CV diseases. It has become the number one killer of non-communicable diseases. The demonization of cholesterol and the touting of studies that show an association of high cholesterol with CV diseases cannot be said to be without vested interests in statin industries. It should also be noted that the benefits of statin are always projected in terms of relative risk reduction as the absolute risk reduction are hardly impressive. It is also high time to realize that there are many studies if not more, that have shown either no association or an inverse association between cholesterol and CV diseases.

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