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A REVISIT TO THE PLASMA CHOLESTEROL LEVELS IN NORMAL AND ABNORMAL CONDITIONS IN THE LIGHT OF RECENT CHOLESTEROL CONTROVERSY

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ABSTRACT
Controversial reports claim that there is no link between plasma total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) and cardiovascular diseases (CVD); rather LDL-C helps in living longer. Denouncing statin therapy, it has been claimed that low plasma cholesterol could be indicative of worsening health condition. With this background, we analysed plasma cholesterol in a mixed middle-class population irrespective of their food habits at Kolkata, India and the mean value was found to be 190 mg/dl. The diabetic subjects without any complications, the diabetic nephropathy patients without any insulin resistance and the coronary artery disease patients with or without defective glucose levels showed the similar pattern of plasma cholesterol when compared with normal control. Diabetic retinopathy patients with insulin resistance only showed a significant higher level of plasma cholesterol. It has been suggested that insulin resistance could increase the plasma cholesterol level by influencing the mechanism by which the HMG CoA reductase system is modulated and controlled by insulin or and the free radical mechanism which is often associated with insulin resistance. It seems that cholesterol lowering drugs be avoided in normocholesterolemic subjects.

KEYWORDS: Insulin resistance, diabetic retinopathy, plasma cholesterol, coronary artery disease.

INTRODUCTION
The role of cholesterol in producing atherosclerotic lesions in the abdominal aorta, carotid and coronary arteries leading to cardiovascular diseases (CVD) has been well confirmed. But the debate whether plasma cholesterol is the true index for assessing such pathological changes still persists. It has been pointed out recently that cholesterol does not predict the degree of atherosclerosis/ coronary artery atherosclerosis as evidenced by autopsy and angiography.[1] The concept of good cholesterol/ bad cholesterol has been challenged. Out of 28 studies, 16 showed lower level of low-density lipoprotein (LDL) was linked with higher mortality while 12 found no linked between bad cholesterol (i.e., LDL-C) and mortality. Controversial reports claim that there is no link between total cholesterol and or bad cholesterol (LDL-C) and heart disease; rather LDL-C helps in living longer. The findings contradicted that cholesterol particularly LDL-C causes fatty build up in arteries.[1] The need for cholesterol measurement even in the older age has been challenged through the measurement had been significantly increased in the population from 2002 to 2012 probably due to excessive use of lipid lowering drugs.[2] Low cholesterol and persistently low cholesterol levels were found to be associated with higher risk of mortality. A spontaneous decline in plasma cholesterol levels was thought to be a dependable marker for worsening health condition.[3]

With the background of these present days' controversies, our objective was to reassess the role of plasma cholesterol in normal population and in abnormal clinical conditions e.g., diabetes and myocardial infraction where the role of plasma cholesterol levels have much stressed.

MATERIALS AND METHODS
All the subjects involved in the project were from middle-class socio-economic status, male, aged between 55 to 70 years with a body mass index (BMI) between 22 and 24.

312 healthy subjects with no manifestation of any disease or metabolic disorders, 178 diabetic patients of Type 2 category non-insulin-dependent diabetes mellitus (NIDDM) of less than 15 years duration without any

complication and 100 diabetic retinopathy patients of more than 15 years duration were selected for the study after a detailed clinical, biochemical and ophthalmological examinations. 145 patients admitted into the hospital with acute myocardial infarction (AMI) whose diagnosis was based on standardised international guidelines, e.g. electrocardiography and cardiac enzymes were also selected for the study. The AMI patients were divided into two groups, e.g. normoglycemic and hyperglycaemic. Diabetic retinopathy patients were also divided into two groups, e.g. insulin resistant and non-insulin resistant. The diabetic patients were asked to take only their maintenance drugs for seven days prior to the experiment. Consents from the patients / subjects along with the approval of the ethical committee of institute were obtained.

A 12 hours fasting blood samples collected from all the subjects in the morning were analysed immediately for plasma glucose and cholesterol by enzymatic methods as described earlier.[4] Insulin in diabetic retinopathy group was measured by radio-immuno assay (RIA) and considered hyper insulinemic when the fasting levels go beyond 20 µIU/ L as described earlier.[5]

RESULTS

The plasma cholesterol levels in different groups did not vary much when compared with normal controls except in the insulin resistant diabetic retinopathy patients where the plasma cholesterol levels were found to be high in comparison to normal controls ($p \leq 0.001$). the results are tabulated in Table 1.

Table 1: Plasma Cholesterol and Glucose in Normal and Abnormal Conditions.

Condition	Number of Subjects	Plasma Glucose (in mg/dl)	Plasma Cholesterol (in mg/dl)
Normal Individual	312	89 ± 10	190 ± 20
Diabetics without any complications	178	178 ± 13	194 ± 29
Diabetic Retinopathy without Insulin Resistant	40	170 ± 18	186 ± 20
Diabetic Retinopathy with Insulin Resistance	60	200 ± 60	208 ± 21
Myocardial Infraction with Normal Glucose	25	99 ± 10	188 ± 25
Myocardial Infraction with Hyperglycaemia	120	126 ± 12	195 ± 25

Values are Mean ± Standard Deviation (SD)

DISCUSSION

For more than half a century, high level of plasma total cholesterol and LDL-C have been considered to be the major cause of atherosclerosis and CVD. Since CVD is one of the leading causes of death in most of the countries, dietary regime and statin treatment to lower the plasma cholesterol levels have been widely promoted though with doubtful benefits.[6] For years dietary cholesterol was implicated in increasing plasms cholesterol levels leading to the elevated risk of CVD. To date extensive research did not show any evidence to support a role of dietary cholesterol in the development of CVD. As a result, the 2015 – 2020 dietary guideline for Americans removed the recommendation of restricting dietary cholesterol to 300 mg per day.[7] Even replacing saturated fat with linoleic acid containing vegetable oil increased mortality rate despite significant reduction in LDL-C and total cholesterol.[8] In an exhaustive review and meta-analysis of 72 dietary studies, it has been concluded that reduced consumption of saturated fat does not reduce CVD mortality.[9] High LDL-C has been found inversely associated with mortality in most people over sixty years. These findings are inconsistent with the cholesterol hypothesis (i.e., that cholesterol particularly LDL-C is inherently atherogenic). Since more than 92% of elderly people with high LDL-C and cholesterol live us long or longer than these with low LDL-C and cholesterol it is pertinent to question the validity of the cholesterol hypothesis and provides the rationale for a re-evaluation of guidelines recommending pharmacological reduction of LDL-C in the elderly as a component of CVD presentation strategies. Particularly claiming benefits from statin treatment exaggeration has to be reconsidered.[10] Even with a plasma cholesterol level of 155 mg/dl, heart attack with 90% blockage in one artery has been reported.[1] A review of research involving nearly 70,000 people found that there is no link between what has traditionally been considered bad cholesterol (LDL-C) and premature deaths of over 60 years old individual from CVD.[11] The cholesterol hypothesis and the efficiency of cholesterol lowering drugs have been questioned because it has failed to demonstrate a mortality benefit. Though cholesterol has been considered as one of the risk factors for atherosclerosis since long, the expectation that CHD could be prevented or eliminated by simply reducing the cholesterol level appears unfounded. The fatal complications of coronary atherosclerosis e.g., thrombotic occlusion, acute myocardial ischemia, lift ventricular dysfunction and malignant arrhythmia are all independent of cholesterol metabolism.[12] It has been reported recently that in CHD plasma cholesterol level did not altered from base level at the onset of attack and

after recovery; more emphasis has been laid on plasma triglyceride and HDL-C level for better evaluation.[13]

Our study is in consonant with some of these recent reports wherein plasma cholesterol level did not deviate from normal level in CHD irrespective of its associated glucose levels. Decades back, it was pointed out that plasma cholesterol and β lipoprotein cholesterol (LDL-C) did not differ in the patients suffering from coronary artery disease (CAD) when compared with the normal controls.[14] One very interesting observation cause out from our study. About fifty years back, it was pointed out in a nutritional experiment are Rajasthan that no difference was observed in plasma cholesterol level between male and female subjects aged between 19 years and 28 years. Their mean value was around 195 mg/dl and 190 mg/dl respectively. The subjects were from middle class families and were vegetarian.[15] In spite of so many guidelines and recommendations for restricting dietary cholesterol and for increasing physical fitness, the plasma cholesterol in wide populations did not alter. In the early part of the contrary, while analysing lipid profile in middle class Bengali population, it was observed that mean plasma cholesterol was around 190 mg/dl. When these subjects were grouped according to their age and sex, no appreciable difference was observed between most of the groups.[16] In the present study, all the groups, except insulin resistant diabetic retinopathy group, showed mean plasma cholesterol levels were around 190 mg/dl. Probably this constancy even in abnormal condition prompted the physicians to give more important to factors like cessation of smoking, change in life style, timely reperfusion leading to improved survival rate and availability of external and implantable defibrillators in the management of CAD than the statin therapy to alter the level of plasma cholesterol.

Besides poor correlation between LDL-C and mortality rate, it has been suggested that presence of insulin resistance is the most important predictor of CHD and Type 2 diabetes.[17] A tendency of arise in plasma cholesterol has been found only in insulin resistant diabetic retinopathy in our study. It has been reported earlier that acute insulin administration enhanced LDL-C susceptibility to oxidation proving that insulin is associated with increased LDL peroxidation independent of the presence of hyperglycaemia. It is possible that insulin resistance is implicated in the genesis and progression of atherosclerotic lesions through positive attendant hyperinsulinemia.[18]

Oxidative stress was found to be associated with diabetic patients where it was maximum in the insulin resistant diabetic retinopathy. The oxidative stress could be almost relieved by dietary natural antioxidant supplementation except in cases of insulin resistance.[6] Statins competitively inhibits the HMG CoA reductase enzyme blocking the conversion of 3 hydroxy 3 methyl glutaryl CoA to mevalonate in the process of cholesterol biosynthesis. The resultant decrease in cholesterol synthesis by 20% – 50% increases a compensatory LDL receptors expression on liver cell and causes increased receptor mediated uptake and catabolism of IDL-C and LDL-C.[2] HMG CoA reductase is a rate limiting enzyme and modulated by insulin or insulin glucagon ratio. Insulin resistance could influence through these mechanisms or oxidative stress leading to increased cholesterol level. It has to be realised that a long-continued suppression of HMG CoA reductase by stations could be disastrous; we still do not have a clear idea about the fate of accumulated HMG CoA in the body.

Ethical approval

Ethical Committee clearance was obtained from Institutional Ethical Reviewed Board of Hospital before commencement of study. Informed consent was obtained from all individual patients included in this study.

Informed consent

Informed consent was obtained from all the participants individually who were included in the study.

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Nil.

Competing interests

The authors declare that they have no competing interests.

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