Serum cholesterol as a risk factor for coronary heart disease revisited

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Abstract

The biology of lipoproteins and lipoprotein particles as mediators of atherosclerosis has been documented extensively. Numerous prospective epidemiological studies have shown a robust relationship between low-density lipoprotein (LDL) cholesterol, or particles bearing apolipoprotein B, and increased risk of coronary heart disease (CHD); and between high-density lipoprotein (HDL) cholesterol or particles bearing apolipoprotein A1, and decreased risk. These relationships are present across the age spectrum and in both sexes. The causality of LDL cholesterol for CHD has been established by the clinical trials on cholesterol lowering and the Mendelian randomisation studies. However, clinical trials that focus on raising HDL cholesterol, or lowering triglycerides, have yielded mixed results, and the Mendelian randomisation studies have generally not supported causality. Research on the effects of diet on serum cholesterol led to public health guidelines, whose implementation within the last five decades was accompanied by lower population cholesterol levels and CHD burden in all of the countries studied. Over the last three decades, the favourable trends in cholesterol levels and CHD have been supported by the increasing use of statin drugs and improved treatments for myocardial infarction.

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Introduction

The trajectory of research on cholesterol has been that epidemiology and basic science informed the need for efficacy trials, which led to clinical and public health guidelines. The implementation of the guidelines led to the curve being successfully turned from increasing to decreasing population rates of cardiovascular disease (CVD). Cholesterol and heart disease are one of the most intensively researched areas of science. Therefore, this review only touches on a few of the topics that are most salient to public health.

Lipids, lipoproteins and lipoprotein particles

Decades ago, the clinical focus changed from total cholesterol (TC) levels to low-density lipoprotein (LDL) cholesterol levels, and high-density lipoprotein (HDL) cholesterol levels, i.e. "bad" and "good" cholesterol, respectively. It is now known that "bad" and "good" cholesterol are actually lipoprotein particles, with the atherogenic "bad" particles comprising the chylomicron remnants from the intestinal absorption of triglycerides and cholesterol, plus very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and LDL particles, all of which derive from hepatic synthesis and the excretion of VLDL cholesterol, with the subsequent removal of triglycerides during circulation to yield smaller, more cholesterol-dense IDL and LDL particles. These particles deliver lipids to the peripheral tissue, and LDL is eventually taken up again by the liver, mainly mediated by binding to the LDL receptor. The "good" HDL particles are also produced and excreted by the liver, take up cholesterol from the peripheral tissue, and exchange cholesterol with the LDL particles. LDL particles are "bad" because they promote atherogenesis, with the particles moving into the intima of the artery through a passive, gradient-driven process, i.e. the more particles there are, the more particles enter the intima. The particles are retained by binding to proteoglycans and undergo oxidation, thereby setting in motion a cascade of factors which lead to endothelial dysfunction.[1] Circulating monocytes adhere to the dysfunctional endothelium and migrate into the subendothelium, where they phagocytose the oxidised LDL particles to form foam cells. The foam cells, debris from dead cells, and deposition of cholesterol crystals form the core of the lipid-laden vulnerable plaques, whose rupture or erosion precipitate an acute coronary syndrome. HDL particles are "good" because they inhibit atherogenesis by promoting cholesterol efflux, and by inhibiting adhesion molecule expression and the oxidation of LDL.[2]

Historically, triglycerides, mainly in chylomicron remnants and VLDL particles; and LDL and HDL cholesterol have been used as

biomarkers. LDL cholesterol was calculated from the measurement of TC, HDL cholesterol and triglycerides. While these remain useful biomarkers, the number of VLDL, LDL and HDL particles can now be more directly measured using nuclear magnetic resonance imaging. The number of LDL particles appears to be more important than the size thereof. Forty-one of 50 studies showed a significant association between LDL particle size and CVD, but only 12 remained significant after multivariate adjustment for other risk factors.[3,4]

On the other hand, all of the four studies that examined the association of the LDL particle number with CVD were significant in both univariate and multivariate models. The measurement of the particle number is not universally available, but the measurement of apoliprotein B for VLDL, IDL and LDL particles, and apoliprotein AI for HDL particles; or even more simply, the measurement of non-HDL cholesterol and HDL cholesterol, provides readily available surrogate measures of "bad" and "good" particle numbers. These can be measured in the fasting or non-fasting state, since they do not depend on the measurement of triglycerides and the calculation of LDL cholesterol. Calculated LDL cholesterol is subject to inaccuracies at high levels of triglycerides and low levels of directly measured LDL cholesterol. Non-fasting samples have an additional advantage in that they better reflect the risk associated with triglyeride-rich remnant particles.[5] The hazard ratios for chronic heart disease (CHD) per standard deviation of non-HDL cholesterol were equivalent to those of the apoliprotein B measurements, and the hazard ratios for the HDL apoliprotein were equivalent to those of the apoliprotein AI measurements in a meta-analysis of 302 430 individuals without prior vascular disease in 68 long-term prospective studies.[6]

Triglycerides, HDL cholesterol and non-HDL cholesterol were significantly associated with CHD in models adjusted for age and sex. However, after further adjustment for several risk factors, HDL cholesterol and non-HDL cholesterol, but not triglycerides, remained significantly associated with CHD. The adjusted hazard ratios for CHD were 0.99 [95% confidence interval (CI): 0.94-1.05], 0.78 (95% CI: 0.74-0.82) and 1.50 (95% CI: I.39-1.61) for triglycerides, HDL cholesterol and non-HDL cholesterol, respectively. The risk of CHD related to non-HDL cholesterol down to levels of 130 mg/dl (3.3 mmol/l), corresponded to an LDL cholesterol of ~80 mg/dl (2 mmol/l). The increased risk for CHD associated with non-HDL cholesterol was evident in all of the age groups, including those aged 70+, in both females and males, and in those with and without a history of diabetes. The hazard ratio for CHD was 1.38, compared to 1.42, for non-HDL cholesterol, in a subset with directly measured LDL cholesterol.

Thus, while LDL cholesterol remains a clinically useful marker for CHD risk, non-HDL cholesterol may be more biologically relevant since it is a proxy for the atherogenic particle number, is not subject to the biases introduced by calculating LDL cholesterol in the conventional assay, and can be measured in both fasting and non-fasting subjects. In these analyses, non-HDL cholesterol was strongly and independently associated with CHD, irrespective of age, sex or diabetes status. Triglycerides were not an independent risk factor in these analyses.

Low-density lipoprotein cholesterol causes coronary heart disease

LDL cholesterol is more than a risk marker. It is also a causal risk factor, as demonstrated by genetic studies and clinical trials. The estimated hereditability of LDL cholesterol is in the range of 40-50%, and a small number of rare monogenic conditions contributing to the hereditability lead to either very high (LDLR, APOB and LDLRAP1) or low (MTTP, APOB, PCSK9) LDL cholesterol levels.[7] The cardiovascular implications of lifelong genetically determined high or low LDL cholesterol levels have been extensively studied in the case of LDL receptor and proprotein convertase subtilisin/kexin type 9 (PCSK9) mutations, respectively. Loss-of-function mutations in the LDL receptor cause familial hypercholesterolaemia (FH), which occurs in 1:500 individuals worldwide, but has a higher frequency of ~1:70 to 1:100 in Afrikaners.[8,9] It has been demonstrated in population-based studies that Afrikaners with heterozygous FH typically have LDL cholesterol levels in excess of 6 mmol/l, and the smaller number of patients with homozygous FH seen in lipid clinics typically have levels of approximately 20 mmol/l. Untreated heterozygous FH is associated with the early onset of myocardial infarction and accounts for roughly one quarter of early-onset myocardial infarction in Afrikaners. In a Japanese study, the average age of myocardial infarction in male heterozygotes was in the third decade of life, and in females in the fourth decade of life. The average age at death was 26 years in homozygotes.[10] Statins block hepatic cholesterol synthesis and increase the number of LDL receptors, thereby lowering LDL cholesterol levels and reducing the risk of myocardial infarction in patients without FH, in patients with heterozygous FH, and also in some, but not all cases, of homozygous FH.

By way of contrast, loss-of-function mutations of the PCSK9 gene are associated with lifelong lower levels of LDL cholesterol and a much reduced risk of myocardial infarction. A 28% reduction in LDL cholesterol was associated with an 88% reduction in the risk of CHD in African Americans in a seminal study by Cohen et al.[11] A smaller 15% reduction in LDL cholesterol in whites due to a different allele was associated with a 47% reduction in CHD risk. The authors concluded that "moderate lifelong reduction in the plasma level of LDL cholesterol is associated with a substantial reduction in the incidence of coronary events, even in populations with a high prevalence of non-lipid-related cardiovascular risk factors". A Mendelian randomisation meta-analysis of the effect of long-term exposure to lower LDL cholesterol, beginning early in life, on the risk of CHD, found that nine polymorphisms in six different genes, including PCSK9, were associated with a consistent reduction in the risk of CHD, which was proportional to the variable reductions in LDL cholesterol associated with individual polymorphisms, and independent of any changes in triglycerides or HDL cholesterol. There was a highly significant 54% reduction in CHD risk for each millimole per litre reduction in LDL cholesterol.[7]

The risk reduction in Mendelian randomisation studies is substantially greater than that obtained by statin treatment started later in life. An average reduction of 24% in the risk of major coronary events

for each millimole per litre reduction in LDL cholesterol from statins over five years was shown in a meta-analysis of statin trials.[12] This individual-level meta-analysis of 90 056 participants in 14 randomised trials on statins showed that the CHD risk reduction was proportional to the degree of lipid lowering obtained, and that significant risk reductions were obtained in patients with and without previous CHD, in older (> 65 years) and younger males and females, whether or not they were on treatment for hypertension or diabetes. Additionally, statin treatment lowered the risk of a stroke and total mortality.

In an updated meta-analysis of an even larger number of subjects (n = 174 149 in 27 trials), the Cholesterol Treatment Trialists' collaborators showed that reducing LDL cholesterol was effective in reducing CHD, even in persons with a low baseline risk (who would not be considered for treatment according to some current guidelines), and that the benefits of statins exceeded the risks.[13] For example, in low-risk subjects with a < 10% five-year risk of major vascular events over five years for every 1 000 individuals, each millimole per litre of LDL cholesterol reduction on statin therapy could result in 11 fewer major vascular events, five more diagnoses of diabetes (and 0.2 fewer major vascular events being avoided because of the risk associated with diabetes), and 0.5 more diagnoses of myopathy and haemorrhagic strokes. In other words, even if diabetes was considered to be a condition that was as serious as a major vascular event, there would be twofold more benefit than risk in low-risk subjects. In high-risk subjects with a 20-30% five-year risk of major vascular events, 28 fewer major vascular events would occur while they were on statin treatment, and there would be five times more benefit than risk.

The findings from the Mendelian randomisation studies and clinical trials, showing CHD risk reductions proportional to the degree of cholesterol lowering and duration of exposure, demonstrate conclusively that LDL cholesterol is a causal risk factor for CHD. In particular, the fact that 88% of CHD events could be avoided by a relatively modest 28% lower lifelong exposure to LDL cholesterol, even in subjects with multiple other risk factors, strongly supports the view that LDL cholesterol is a sufficient risk factor, i.e. no other factor needs to be invoked to explain the greater part of CHD risk. By way of contrast, the Mendelian randomisation studies and clinical trials have not provided conclusive support for causality in the cases of triglycerides or HDL cholesterol.

Implementation

Public health and clinical guidelines, based on knowledge of the effects of diet and statins on serum cholesterol, and the relationship of serum cholesterol to CHD risk, have been effective in lowering population cholesterol levels and CHD risk in many countries. One of the more striking examples is from Finland, which towards the end of the 1960s, had the highest CHD mortality in the world. However, over the course of 30 years, changes in diet were encouraged using a population strategy, especially with regard to the type and amount of fat consumed, with an emphasis on the intake of fresh vegetables and fruit. The result was an 80% reduction in the rate of CHD death.[14] Seventy-five per cent of the CHD risk reduction was attributable to changes in lifestyle, and in particular, the 21% lowering of serum cholesterol levels. Deaths due to heart disease, including heart failure, in the USA, increased steeply from 1900-1970, after which they levelled off and started dropping in 1990.[15] The decline in CHD death rates in the USA has been equally impressive, with a 70% decline from 1970-2000. The major reason for the slower decline in total heart disease, than in that for CHD deaths, is that deaths from heart failure have continued to be high because CHD case fatality rates have improved, leaving a larger number at risk of developing heart failure. The decline in CHD was preceded by lowering the population dietary fat intake, particularly that of saturated fat, from 1965 onwards, accompanied by the lowering of population serum cholesterol levels.[15,16] The changes in population fat intake were preceded by the publication in 1957 by the Framingham Heart Study in which serum cholesterol was established to be as a risk factor, as well as a series of publications from the Anti-Coronary Club study, which showed the cholesterol-lowering effect of what was dubbed the "prudent diet" (30% total fat with approximately one third of each of the polyunsaturated, monounsaturated and saturated fats), plus recommendations from the American Heart Association and the American Medical Association encouraging the use of a "prudent diet" in high-risk patients.[17-19] These recommendations were incorporated in the 1977 dietary goals for Americans.[20]

The authors of the dietary goals, noting the decreasing intake of fruit, vegetables and wholegrains, and the increased intake of meat, fat and sugary drinks over the preceding 50 years, made recommendations to:

- Increase the consumption of fruit, vegetables and wholegrains.
- Decrease the consumption of meat, and increase the consumption of poultry and fish.
- Decrease the consumption of foods high in fat, and partially substitute polyunsaturated fat for saturated fat.
- Substitute non-fat milk for whole milk.
- Decrease the consumption of butterfat, eggs and other high-cholesterol foods.
- Decrease the consumption of sugar and foods high in sugar content.
- Decrease the consumption of salt and foods high in salt content.

The advice to reduce total fat intake would necessarily lead to an increase in carbohydrate intake, and this is what happened in many countries. More recent guidelines place less emphasis on total fat intake, and more on the quality of fat and that of carbohydrates.[21] Nevertheless, it is likely that the dietary goals further assisted in the already ongoing decline in CHD risk in the USA. Public recommendations in the UK lagged behind those in the USA. Declines in total fat consumption occurred in the mid 1970s and subsequent declines in CHD death rates were delayed to the mid 1980s.[22] More recently, the introduction of statin drugs in the late 1980s and the improved treatment of coronary disease have maintained the downward trajectory in CHD mortality. Approximately half of the decline in CHD mortality in the USA may be attributable to reductions in major risk factors, and roughly half to improved treatment.[23]

Conclusion

The principal conclusion of this brief review is that cholesterol levels are associated with the increased risk of coronary heart disease, even at "normal" levels of cholesterol, in both men and women of all ages. Biology, in the form of genetic studies, supports the causal role of LDL cholesterol, as does the fact that the treatment of elevated levels reduces risk in individuals. Finally, the adoption of knowledge on the dietary effects of serum cholesterol and the improved management of elevated levels has led to declines in the CHD population risk.

Declaration

The views expressed in the article do not necessarily represent the views of the National Heart, Lung, and Blood Institute, nor the United States Department of Health and Human Services.

Conflict of interest

The author declares that there were no conflicting interests which may have inappropriately influenced him when writing this article.

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