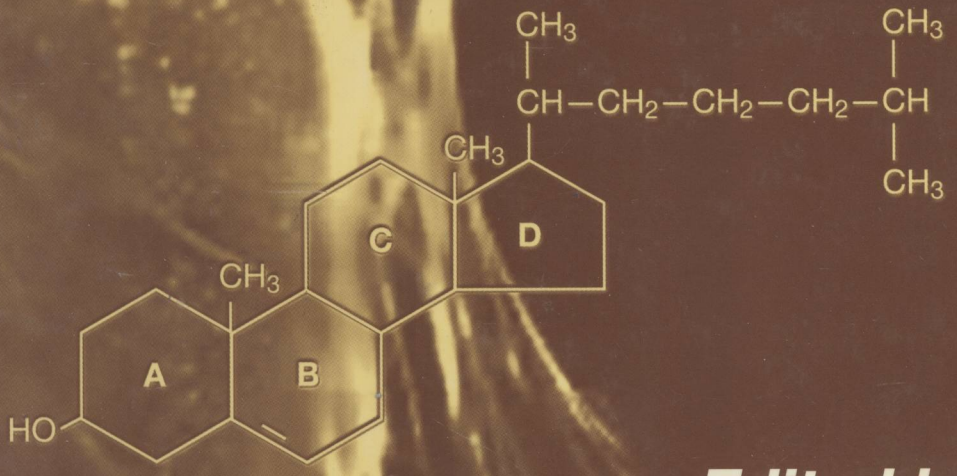
Lipid Metabolism and Health



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Lipids and Health: Past, Present, and Future

Bryant A. Stamford and Robert J. Moffatt

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Introduction

The German philosopher, Arthur Schopenhauer (1788–1860), once said that when new ideas are first introduced they are likely to be dismissed out of hand, then ridiculed, and finally, accepted as self evident. This natural progression is particularly applicable to the scrutinizing mind of the scientist who must dismiss new ideas as unacceptable, thus ensuring that acceptability will occur only when ample empirical evidence is provided. The acceptance of serum cholesterol as causally related to coronary artery disease (CAD) has traversed just such a gauntlet, and is now accepted as self-evident. Moreover, vigorous research efforts have revealed a relationship and interactions that are substantially more complex than imagined when this concept was introduced more than a half century ago.

In the 1930s, medical researchers were aware that extraordinarily high levels of serum cholesterol were associated with pathology. Xanthomatosis was known to be related to symptoms of heart disease (angina pectoris) and likely was a contributor to myocardial infarction.[1] Such cases were rare, however, and a relationship between cholesterol and CAD in those with

high, but lesser, levels of cholesterol was dismissed. This, even though it was known that cholesterol was found in atherosclerotic lesions in persons not suffering from xanthomatosis. The cholesterol in lesions was considered to be incidental, as the lesions were, it was assumed, caused by degenerative alteration of the arterial wall.

At the time, the normal range for cholesterol was determined in the similar manner employed to judge other blood-borne components. The mean of the general population was assessed, standard deviations were calculated, and the normal range extended from minus two standard deviations of the mean, to plus two. This meant that only those individuals with blood cholesterol levels beyond two standard deviations above the mean were diagnosed as hypercholesterolemic.

The normal range extended to 300 mg/dl (7.76 mmol/L), and, thus, only approximately 2.5% of the population would be viewed as having a dangerously high level of cholesterol (greater than 300 mg/dl). And, given the tendency of practitioners to allow older patients a greater margin of error, it was not uncommon to extend the normal range by 10% in those at or above retirement age. Thus, persons 65 and older could be told that their cholesterol test results were "normal," notwithstanding an incredibly high level, reaching 330 mg/dl!

This interpretation logically excused serum cholesterol as a causal factor in CAD, because while only a tiny fraction of patients were labeled as hypercholesterolemic, legions were dying of CAD. Moreover, factors including cigarette smoking, high blood pressure, and diabetes had been identified and indicted as causal, pushing cholesterol further into the background. The well-respected 1948 text, *Quantitative Clinical Chemistry*, by Peters and VanSlyke[2] stated the case unequivocally: "There is no satisfactory evidence that the incidence of atherosclerosis bears any relationship to the concentration of cholesterol in the blood."

Once a seed is planted and takes root, it is difficult to stamp it out completely, even though the strength of evidence to the contrary is formidable. Indeed, today, although the role of cholesterol in the progression of CAD is taken for granted, not long ago offspring of the original seed continued to flourish, and many still questioned the extent of impact of cholesterol on atherosclerosis. And among those who accepted the basic premise, it was not clear that reducing cholesterol reduced mortality from CAD; and if it did, how much reduction was required? In addition, if there were a bona fide relationship, was the use of powerful medications warranted, or did available medications impose risks that were greater than those imposed by the high level of cholesterol itself?

The Cholesterol Risk Factor

The Framingham Heart Study was the key to elevating serum cholesterol to the status of CAD risk factor.[3–5] Thousands of men and women were studied prospectively and it was determined that, indeed, a relationship exists between cholesterol and CAD. As the concentration of blood cholesterol increases, the risk of CAD increases as well, the risk relationship defined as a continuous and curvilinear function (of the concentration of blood cholesterol). Many additional large-scale studies solidified the Framingham findings.

Despite the volume of data supporting blood cholesterol as problematic, skeptics required data supporting positive outcomes arising from intervention. Specifically, if cholesterol is a risk factor for CAD, reducing the concentration of cholesterol in the blood should reduce risk. The first step was determining safe and effective ways to reduce cholesterol. Dietary and drug intervention was studied and found to be effective.[6–9] Results from the Coronary Primary Prevention Trial[10] demonstrated that a drop in blood cholesterol of 9% reduced CAD risk by 19%. Results of this study combined with several others gave rise to national guidelines that replaced use of the "normal range" approach.

Impetus for change can be credited largely to efforts of the National Cholesterol Education Program (NCEP), launched by the National Heart, Lung and Blood Institute (NHLB) of the National Institutes of Health (NIH) in 1985. New guidelines set stricter goals as blood cholesterol levels below 200 mg/dl were deemed "healthy" and desirable, while those exceeding 240 mg/dl were viewed as clinically significant. Awareness of the risks associated with hypercholesterolemia increased greatly thanks to efforts of the NCEP and by 1995, 70–80 million more Americans sought to have their blood cholesterol concentrations determined, a 40% increase in ten years.

The above guidelines have been in place for nearly two decades. Many experts argue that such guidelines, while an improvement on the "normal range" approach, are far too liberal (given that the average total cholesterol level in the U.S. is 205 mg/dl). Moreover, such guidelines are viewed as deficient in many ways, particularly when considering the interplay between cholesterol and other risk factors. In addition, ample evidence has accumulated in recent years attesting to the clinical efficacy of so-called "statin" drugs to dramatically overhaul the cholesterol profile and, in turn, reduce the incidence of heart attacks and CAD deaths.

It would appear that continual redefining of guidelines would be the order of the day as new evidence accumulates. However, it must be taken into consideration that the creation, establishment, and acceptance of new guidelines add up to a ponderous and painstaking process. And when new guidelines are introduced, confusion often reigns because, in effect, at least for a while, two (or more) sets of guidelines are operating. The older guidelines continue to be followed faithfully by many practitioners on the front lines,

while news of updated guidelines is disseminated directly to the public through various media outlets. Confronting such ominous circumstances ensures that the approach to new guidelines is calculated and cautious in the extreme.

This is a universal dilemma and is not peculiar to cholesterol. Serum triglycerides have traversed similar terrain. Traditionally, serum triglycerides have been viewed as lacking clinical significance until reaching 275–300 mg/dl, and even then there was some question as to the importance of such elevated levels. This is akin to the previous acceptance of the "normal range" criterion for cholesterol values. While it was known that triglycerides are adversely impacted by increased body fatness and uncontrolled diabetes, the facts that the role of triglycerides in CAD is controversial, and triglycerides are not recognized as an independent CAD risk factor, have inspired continued tolerance of such high levels.

Most recently, however, as metabolic syndrome has attracted increased attention, and owing to exploration of definitive diagnostic strategies, serum triglycerides seem to have elevated in status, leading to a tightening of guidelines. Diagnostic criteria for metabolic syndrome have been set forth that include a cluster of five characteristics. One of these is serum triglycerides (fasting) in excess of 150 mg/dl.

Regarding serum cholesterol and triglycerides as important health threats, each has gone through a stage of benign neglect in which very high levels were considered "normal." And now, each has captured the spotlight with emphasis focused on reducing levels to a fraction of what was previously deemed acceptable.

Efforts have been ongoing to further improve upon cholesterol guidelines for clinicians. New cholesterol guidelines have been proposed that address the need for placing blood cholesterol levels within the context of a global heart disease risk profile.[11] A risk score is computed referencing the probability of a heart attack within 10 years. The new guidelines recommend recurring assessment at five-year intervals beginning in young adulthood. Efforts in this direction not only broaden the scope of factors considered, they also have enhanced the sophistication of risk analysis by requiring a lipoprotein profile. Attention also has been focused on the interaction of serum triglycerides and lipoproteins.

Lipoproteins

Cholesterol is insoluble and, therefore, transportation of cholesterol in the blood is challenging. Over the years, considerable research has been conducted on cholesterol transport.[12–14] It was found that cholesterol is transported in combination with other substances as lipoproteins, with a hydrophobic lipid core, and a surrounding layer of apolipoproteins and

phospholipids. The apolipoproteins were found to vary in size and density (labeled as high, low, and very low), and this, in turn, was found to be significant in determining the metabolic fate of the complex.[15–17]

The relative proportion of alpha (high-density HDL) to beta (low-density LDL) lipoproteins was found to be critical to the cholesterol/CAD relationship. The fraction of blood cholesterol transported as LDL contributes to atherosclerosis, whereas HDL is inversely related to risk. Vigorous research efforts have uncovered several more classes and subclasses of lipoproteins.[18] For utilitarian reasons in the clinical setting, the ratio of total cholesterol to HDL typically is employed, because direct assessment of LDL is difficult, and there exists a high correlation between LDL and total cholesterol.

But still, many questions remained unanswered as numerous exceptions to the rule surfaced. Intermediate-density lipoproteins (IDL) have been found to increase CAD risk, especially when IDL is the major lipoprotein.[19] Very-low-density lipoproteins (VLDL) also may be influential. However, the role of VLDL may be important because of the inverse relationship with HDL, and may reflect metabolic disorders (insulin resistance and diabetes, for example), rather than a direct impact.[19]

Despite progress, many inconsistencies associated with the prediction of CAD risk based upon serum cholesterol levels and the blood lipid profile remained. For example, if all risk factors are equal (or reasonably so), why is it that individuals with similar levels of LDL can have substantially different levels of risk for CAD? This would seem to be inconsistent with the notion that LDL entrance into the interior arterial wall (the endothelium) is gradient driven. The more LDL that is present the more interaction there will be between LDL and the arterial wall, resulting in greater LDL penetration of the endothelium, greater oxidation of LDL, and thus greater atherogenesis.

Unexplored until recently is the size and density of lipoprotein particles, and such explorations offer revealing insights.[20,21] At any given level of serum LDL, the size and density of LDL particles may be the determining factor that promotes CAD risk, because small, dense particles may enter the arterial wall more readily than larger, "fluffy" particles.[22,23] Those with small LDL particles have a substantially larger number of LDL particles and, thus, despite equal levels of serum LDL, gross differences in the particle size and density would appear to preserve the gradient driven aspects of atherogenesis. Unfortunately, when assessing LDL with a conventional blood lipid profile approach, the size and density of LDL particles escapes detection.

HDL is responsible for reverse cholesterol transport — the removal of cholesterol from developing lesions, which would reduce CAD risk.[24] Enzymes carried by HDL may also play a protective role, acting to retard oxidation of LDL (discussed below).[25] This would suggest that a high level of HDL is always helpful, and that a low level of HDL is always destructive. This is not the case, however, as inconsistencies have again been observed.

Particle sizing may be relevant to HDL as well as LDL and may help to explain some of these inconsistencies.[22,23] Larger HDL particles may be more effective in reverse cholesterol transport, and may interfere with interaction

between LDL and the endothelium. Smaller HDL particles may be ineffective in this regard. Moreover, small HDL particles may actually contribute to atherosclerosis. Thus, a patient with a preponderance of larger HDL particles may be at lower risk than another patient with fewer large HDL particles, even though conventional blood lipid assessment reveals that the two are equal on the HDL scale.

Particle sizing may also have relevance with regard to VLDL.[22] Larger VLDL particles may increase CAD risk, because when insulin resistance is present, excess carbohydrate increases production of triglyceride. This results in VLDL that are loaded with triglyceride, which can lead to metabolism of large VLDL particles into small LDL and small HDL which, in turn, can promote atherosclerosis.

Atherosclerosis

The "injury" hypothesis of atherosclerosis was proposed by Ross in 1970.[26] The driving event in the process was thought to be damage to the endothelium, progressing to denuding of the delicate endothelial lining, and eventually progressing to the status of fibrous plaques. Major emphasis of the injury hypothesis was placed on smooth muscle proliferation.

Attention was focused on fatty streaks and the foam cells loaded with lipids. Because of the emphasis on smooth muscle proliferation, it was assumed that fatty streaks, the earliest of lesions, were associated with foam cells that were derived from smooth muscle cells exclusively. Later, it was determined that while some foam cells originate from smooth muscle, most arise from monocytes in the bloodstream. This finding challenged the injury hypothesis, because monocytes can penetrate an intact and functioning endothelium where they take up residence as macrophages and attract cholesterol.

Subsequent research efforts by Ross and Glomser[26] and others postulated the utility of both hypotheses — the endothelial injury, and monocyte (lipid infiltration) hypotheses in the progression of atherosclerosis.[27,28] Cholesterol may enter an uninjured endothelium that is fully functioning, and this could lead to the accumulation of foam cells. Damage to the endothelium may result, owing to secretion of local factors (such as cytokines and growth factor), and to an inflammatory response. This, in turn, would promote fibrous plaque development.

Progress in defining the steps of atherosclerosis was stymied, however, when it was discovered that isolation and incubation of monocytes in a medium loaded with cholesterol did not cause the monocytes to soak up cholesterol, and thus produce foam cells.[29] The same finding occurred with smooth muscle cells. This led to research that revealed the need for alteration of cholesterol prior to being taken up and accumulating. The cholesterol must experience oxidative damage.[30] In turn, animal research has indicated

that antioxidants can retard progression of lesions substantially.[31] Research efforts into the impact of antioxidants (specifically vitamin E) in humans is ongoing, with mixed results.[32]

Integrity of the endothelium is a hot topic currently. Improved endothelial function has many advantages in that platelets and inflammatory cells are less likely to adhere, and the natural balance between locally derived vasodilating and vasoconstricting substances is preserved. Nitric oxide (NO) is a natural vasodilator, and it has been reported that in the presence of endothelial dysfunction, there is a paradoxical vasoconstriction response to vasodilator substances. This may be an important factor in initiating atherosclerosis.[33]

With all of the complexities associated with initiation and progression of atherosclerosis, it is clear that several factors conspire, conflict, and contribute. At first glance, it might appear that as the research movement in this area advances, the role of blood lipids has been demeaned. The role of a dysfunctional endothelium, the impact of NO, and the intricacies of the inflammatory response, have seized the focus. However, blood lipids retain their position in the spotlight as several studies have reported improved endothelial function when blood lipids are reduced.[34–36] And a profound and acute improvement in endothelial function was observed following LDL apheresis.[37]

Past, Present, and Future

Historically, in Japan decades ago, dietary fat intake was low, serum cholesterol levels were low (160 mg/dl),and the incidence of CAD was low.[38] This, despite a high incidence of hypertension and the immense popularity of cigarette smoking. Is it possible that a very low cholesterol level precluded atherosclerosis and development of CAD, even in the face of other significant CAD risk factors? Is there a protective threshold for cholesterol, and LDL in particular? Or, are other factors operating that have yet to be uncovered and elucidated.

Much still needs to be determined in the realm of lipoproteins and their role in promoting atherosclerosis, such as the role of lipoprotein (a), and specifics surrounding the increased risk associated with high serum triglyceride levels and low HDL. Further examination is needed of the notion that at any given level of serum LDL, the size and density of LDL particles may be the determining factor that promotes CAD risk. Particle sizing may be relevant to HDL as well as LDL, and may help to explain some of the current inconsistencies. A better understanding of homocysteine, HS-Crp, as a marker of the inflammatory response, the nature of receptor activity, the significance of nitric oxide, and elucidation of the roles of cytokines and

growth factors, may lead to revision of current hypotheses and creation of new clinical strategies.

Lipids and Health

The purpose of this volume is to provide an overview and historical perspective of the evolution of serum lipids and lipoproteins from a mere curiosity, to acceptance as an established and major CAD risk factor, and, ultimately, to formulation of present clinical guidelines. Speculation regarding future developments and the further potential evolution of guidelines will be discussed.

Considerable attention has been focused on the fundamentals, such as basic lipidology. Lipids are the structural components of all living cells, and they play a number of critical roles. Lipid/lipoprotein metabolism is discussed with regard to the regulation, absorption, synthesis and excretion of cholesterol. The biology of atherosclerosis emphasizes arterial adaptations and the inflammatory response, as well as the impact of atherosclerosis on cerebral vascular and peripheral artery disease. A chapter on endothelial function as impacted by nitric oxide and exercise is included.

Clinical methodologies for measuring lipoproteins are a critical consideration given the many challenges associated with accurate determination of the number and size of circulating LDL (and HDL) particles and the CAD risk they confer. A critique of commonly employed assessment techniques and the implications of their potential inaccuracies is discussed. Clinical strategies, with emphasis on pharmacological treatments, are discussed with regard to managing unhealthy lipid levels.

Lipids and lipoproteins can be impacted by a number of factors, including obesity, diabetes and metabolic syndrome, diet/nutrition, exercise (acute and chronic effects), cigarette smoking and environmental tobacco smoke, alcohol consumption, heredity, age, gender, and race. These factors are discussed in detail.

In summary, the relationship between lipids and CAD risk is well established. The complexities associated with this relationship are continually being revealed and addressed, which has, among other things, instigated a shift toward more aggressive clinical management of unhealthy lipid levels. This is a highly positive step, and represents the first prong of a comprehensive approach. The second prong entails primary preventive intervention strategies that include emphasis on improving a variety of lifestyle factors (weight management, healthy dietary practices, daily exercise, etc.). Progress in these areas is greatly needed and is critical to reducing the incidence of the number one cause of death in the industrialized world today.