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The mainstream hypothesis that LDL cholesterol drives atherosclerosis may have been falsified by non-invasive imaging of coronary artery plaque burden and progression

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SUMMARY

That LDL cholesterol drives atherosclerosis is a widely if not almost universally held belief, and this belief strongly influences the mainstream approach to coronary heart disease. However heart disease has a number of stages, and in terms of primary prevention, the initiation and progression of silent or sub-clinical atherosclerosis is clearly fundamental. However, studies that address the efficacy of interventions and practices aimed at the primary prevention of heart disease almost always use event-based endpoints such as fatal or non-fatal myocardial infarction or unstable angina. These endpoints do not directly relate to the primary prevention of silent atherosclerosis and to apply these results to asymptomatic individuals in this context involves an extrapolation.

The advent of non-invasive imaging techniques which allow the determination of coronary artery plaque burden and progression of plaque has provided a unique opportunity to examine the relationship between both traditional and emerging risk factors and the extent of sub-clinical coronary artery disease and in particular allow the testing of the hypothesis that LDL cholesterol drives coronary atherosclerosis. Consistent with earlier autopsy studies, the use of electron beam tomography and contrast enhanced CT angiography techniques have created a large body of evidence which appears to falsify this hypothesis. The large number of null results for the association between serum LDL cholesterol levels and the prevalence or progression of both calcified and non-calcified plaque in the appropriate vascular bed and involving large numbers of men and women over a wide range of age, ethnic background, plaque burden and cholesterol levels cannot be easily dismissed. If the hypothesis is false, this has a significant impact on currently held views regarding risk factors and therapeutic interventions in the case of individuals who are asymptomatic, that is, issues associated with primary prevention. Also, if the hypothesis is false, then the use of changes in LDL as a surrogate marker for judging the importance of various risk factors for silent atherosclerosis and thus coronary artery disease can be called into question.

Introduction

Progress in science depends not only on hypothesis generation but also on hypothesis falsification. Cholesterol and in particular LDL has been called the *driving force of atherosclerosis* [1]. But this widely held view is based almost entirely on studies with cardiac event endpoints rather than a direct measure of coronary plaque burden. If this hypothesis happens to be false there are significant ramifications related to coronary heart disease (CHD), especially in primary prevention.

Most primary prevention studies focus on event endpoints, generally in moderate or high-risk patients, rather than sub-clinical coronary atherosclerosis judged by plaque burden, prevalence and progression. Such studies provide limited or even misleading guidance as to the prevention of the primary disease process itself, since the mechanisms involved in the incidence or progression of atherosclerosis differ in many respects from those involved in the triggering of acute coronary events. Furthermore, implicit or explicit extrapolation of study results from high-risk individuals or even those with symptomatic CHD to asymptomatic individuals judged free of CHD is not uncommon and is open to question.

As will be documented below, there is a growing body of literature suggesting that the traditional lipid risk factors appear to offer little or no information regarding coronary plaque burden. In fact, extensive data continues to accumulate indicating that, contrary to the conventional wisdom, total cholesterol (TC) and LDL cholesterol in asymptomatic individuals are not associated with either the extent or progression of coronary plaque, as quantified either by electron beam tomography (EBT) or coronary CT angiography. Since conventional lipid risk factors fail to

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identify significant numbers of individuals with extensive plaque burden and also fail to identify many with zero or low plaque burden, imaging can lead to reassignment of risk categories, both up and down, and can identify individuals who by traditional assessment qualify for therapy when none is in fact indicated [2]. When enhanced risk is identified by quantifying coronary plaque burden, it appears to be almost universally an indication for applying the current treatment algorithms. This brings into question the proposed approach, in the context of primary prevention, that calls for LDL targets as the central and in many cases the only therapeutic response to the enhanced risk represented by presence of significant coronary plaque [3,4]. If total and LDL cholesterol are not associated with the incidence, prevalence or progression of subclinical coronary atherosclerosis, then to follow this path for appears equivalent to adopting a protocol that is neither evidence-based nor intuitive.

Some inconvenient questions

If the hypothesis is true that LDL is the driving force of atherosclerosis, one might expect to find statistically and clinically meaningful correlations between LDL cholesterol levels and the extent and progression of atherosclerosis as measured by coronary artery plaque. The same would be expected for TC, which is generally regarded as an adequate surrogate for LDL. Extensive evidence, mostly based on LDL, suggests otherwise. Studies in fact give rise to a set of rather inconvenient questions. Thus if the hypothesis is true one can ask:

- Why do autopsy studies of the correlation between the extent of coronary atherosclerosis and serum cholesterol yield null results? The answer that the blood samples, mostly from accident or suicide victims, were obtained too long after death has been discredited, and there appears to be no reason to suspect that these studies were carried out either incompetently and with selection bias [5].
- Why did Hecht et al. [6] find that total TC, LDL, and HDL cholesterol did not correlate with either the extent or prematurely of calcified plaque burden in 1105 consecutive, asymptomatic individuals self-referred for EBT?
- Why did Hecht et al. [7] fail to find no correlation between LDL and the coronary calcium percentile (correlation coefficient 0.06 with a scatter plot showing no visible correlation) for 304 asymptomatic women? In fact, they found no correlation between either the calcium percentile or score and any lipid measurement.
- Why when 1653 men and women without a history of CHD were subjected to coronary CT angiography using contrast media did Johnson et al. [8] fail to find a correlation between total plaque burden (calcified, mixed and non-calcified) and total serum cholesterol (Spearman's rho = −0.04), a result the authors indicate agreed with other studies?
- Why in a study of the impact of psychosocial factors on coronary calcification in a large group of male and female asymptomatic individuals ($n = 780$), was there no correlation between TC or LDL and the calcium score with Spearman correlation coefficients near zero? Multivariate analysis gave an odds ratio of 1.005 for LDL [9].
- Why did Arad et al. [10] in the St. Francis Heart Study find no correlation ($r = 0.03$, $p = 0.15$) between LDL levels and coronary calcium scores in 4903 asymptomatic individuals?
- Why for adults with familial hypercholesterolemia, did Jensen et al. [11] find that age-adjusted coronary calcium scores were not associated with cholesterol levels as assessed by either scatter plots or correlation coefficients?
- Why did Kronmal et al. [12] find among approximately 2900 individuals that the relative risk of incident coronary artery calcium associated with LDL was only 1.03 per 10 mg/dL and barely reached statistical significance (lower CI 1.01) whereas both HDL and triglycerides exhibited much stronger associations?
- Why did Sung et al. [13] in a recent study of coronary calcium scores and estimated coronary risk (Framingham), find negligible correlation between LDL or TC and calcium scores in 1653 asymptomatic individuals judged free of CHD (Spearman's coefficient = 0.07 and 0.08, respectively). Even the correlation coefficient of 0.26 found for the log calcium score vs. 10 year absolute risk estimate yielded a scatter plot suggesting that this magnitude of correlation, which was three to four times greater than that found for LDL and TC, had no clinical utility.
- Why in a study of 177 asymptomatic patients of intermediate risk of CHD did Ramadan et al. [14] find a null result (OR = 1.022, $p = 0.361$) for the odds of positive coronary calcification outcome and LDL in a multivariate model? The group studied had a wide range of both LDL levels and calcium scores.
- Why were Takamiya et al. [15] unable to find any association whatsoever between LDL and coronary calcium in three multiple logistic regression models when 100 asymptomatic individuals underwent EBT.
- Why do studies that looked for a correlation between TC or LDL and the progression of atherosclerosis find no statistically significant association [12,16–24]? All 10 studies involved EBT. Lack of association was indicated by absence from multivariate analysis or absence or non-significant association in comparisons of progression vs. no progression, or non-significant results in univariate or multivariate analysis. Most studies examined the correlation with LDL as well as TC.

These questions directly address coronary plaque and thus do not involve arguments based on studies of atherosclerosis in other vascular beds. Furthermore, the correlation between carotid artery intima-media thickness and coronary atherosclerosis is modest, especially in asymptomatic individuals or those merely suspected of CHD where correlation coefficients range mostly between 0.2 and 0.3 [25].

It might be argued that total plaque rather than calcified plaque should be the basis for judging the hypothesis. While one study cited in the above questions did indeed look at total plaque, several studies have found that non-calcified plaque represents a small fraction of the total plaque burden [26–28]. Also, eight studies involving over 27,000 asymptomatic patients found that those with zero calcium score had an average annual coronary event rate of only 6.6 per 10,000 individuals [29], and as the calcium score increases, so does the risk of adverse coronary events [2]. Thus arguments based mostly on EBT scans appear relevant.

It might be argued that it is oxidized LDL that is driving atherosclerosis. One model of atherogenesis includes small dense LDL particles penetrating into the vascular wall where they are oxidized and lead to the formation of macrophage-derived foam cells. Oxidized LDL is also though to be involved in the initiation of endothelial dysfunction [30]. Oxidized LDL appears to be associated with coronary calcification. The presence of zero, intermediate or high levels of coronary calcification were associated with progressively and significantly higher circulating levels of oxidized LDL [31]. However, oxidized LDL mainly resides in the vascular wall, and has a short half-life in the circulation. Oxidation of LDL in the circulation is considered unlikely due to adequate antioxidants [30]. Thus what is detected in the circulation presumably comes mainly from the vascular wall and represents mostly a steady state between leakage and removal.

Attempts to relate circulating oxidized LDL with conventional risk factors in asymptomatic and even symptomatic individuals

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have been inconsistent [31,32] with the studies using the most selective assay finding no association with hypertension, hypercholesterolemia, diabetes or smoking [32,33]. Thus what is currently known about oxidized LDL does not appear to weaken the body of evidence related to the hypothesis that LDL drives atherosclerosis, since operationally, it is the circulating LDL that is measured and targeted and oxidized LDL makes up a very small fraction of total circulating LDL and does not correlate with it [30,32]. Also, small, dense LDL particles also make up only a small fraction of the total circulating LDL in individuals without so-called dyslipidemia associated with elevated triglycerides and low HDL, and the amounts appear independent of the presence or absence of elevated cholesterol [34].

Implications and discussion

LDL as a surrogate endpoint for CHD risk

For example, a diet high in saturated fat is widely believed to be atherogenic and to operate by raising LDL and thus stimulating atherosclerosis. The above results do not support this argument. The fat-cholesterol hypothesis was the basis of the original objections to both dietary fat and carbohydrate-restricted diets, and it is also part of the justification for standard guideline recommendation to limit fat intake and saturated fat in particular. Also, as Accurso et al. point out, inconsistent with this guideline is the observation that increased saturated fat intake leads to an *decrease* in small dense LDL, and greater intake in saturated fat was in a recent study found to be associated with *reduced* progression of coronary arthrosclerosis [35]. The role of saturated fat in CHD was already challenged in 1998 [36].

Determinants of plaque progression

In ten coronary plaque progression studies cited above [12,16–24], the prior existence of calcified plaque and hypertension were the most frequently found statistically significant positive risk factors, followed by diabetes, lipoprotein(a), triglycerides, smoking, the Framingham risk score, and HDL (negative association), but these latter factors were not consistently identified. In terms of modifiable factors, the only strong association consistently found was with hypertension. Also, in a study that started with individuals having a zero calcium score, only hypertension was a significant modifiable risk factor [20].

Plaques and lipid lowering

The null results from the 19 trials cited above suggest that lowering LDL would have no impact on the prevalence or progression of coronary plaque and calls into question the proposed approach which targets LDL for asymptomatic persons of intermediate traditional risk of CHD who have an elevated calcium score [3,4]. Several randomized clinical trials employing statins and enrolling asymptomatic individuals support this inference. Two compared different levels of a statin and two were placebo controlled. The placebo controlled studies found that statin therapy had no effect on the progression of coronary calcification as measured by the calcium score [37,38]. In the randomized trials comparing doses or different statins, atherosclerosis progression as measured by calcified plaque showed no relationship with on-treatment LDL levels and intensive therapy was unable to attenuate coronary artery calcium progression [38–40].

It is interesting in view of the JUPITER lipid lowering and CRP trial [41] that three recent studies directly examined the correlation between the coronary calcium score and high-sensitivity CRP (hsCRP) levels and found that there was no association [17,42,43]. These results are consistent with JUPITER'S event-based endpoints, and suggest that the JUPITER protocol may not be impacting silent atherosclerosis. Another study found that coronary calcium did not identify the same risk group as hsCRP and that the tests did not appear to be interchangeable when selecting individuals for more aggressive therapy [44].

Invasive studies that found statin therapy causes slowing of progression or a reversal of coronary atherosclerosis might be considered as a source of a counter argument to the views presented above. But these studies are invasive and of necessity require individuals with angiographic proven coronary heart disease or individuals with symptoms in order to justify the associated risks [45–47]. These studies generally involve following volume changes in one target segment. They do not generate a calcium score and the extrapolation of the results to asymptomatic individuals and individuals without established CHD does not appear justified, especially when for this group, statin treatment produced null results in randomized clinical trials where coronary plaque burden was measured. Also, in the invasive imaging studies, the clinical significance of small changes in atheroma volume has been questioned [48]. If lipid lowering studies involving invasive imaging are presented as evidence for the hypothesis that LDL drives atherosclerosis, then aside from the issues raised above, it is incumbent on those using this argument to prove that the drug is not producing the effect by one or more of the many pleiotropic effects attributed to statins and the decrease in LDL is other than incidental [49]. In fact it can and has been argued that this caveat should apply to any result produced by a statin, given the large and growing number of pleiotropic effects associated with this class of drug.

The results reviewed above may seem somewhat paradoxical since a number of studies, Framingham being the most prominent, find that total cholesterol is a risk factor for CHD event endpoints [50]. However, as de Lorgeril and Salan have recently pointed out [51], the risk of sudden coronary death is independent of TC and LDL, and sudden coronary death accounts for over 50% of all cardiac mortality. They also review primary prevention lipid lowering studies up to 2006 and point out that this intervention has either a non-significant or very small absolute effect on overall mortality, but lipid lowering decreases significantly the risk of non-fatal complications of CHD. They indicate an urgent need for a scientific explanation.

Conclusions

These inconvenient questions, which are based 19 studies, unless provided with satisfactory evidence-based answers, appear to falsify the hypothesis that LDL cholesterol is the driving force behind atherosclerosis. This large number of null results based on direct observation of both calcified and non-calcified plaque in the appropriate vascular bed, and involving large numbers of men and women over a wide range of age, ethnic background, plaque burden, and cholesterol levels cannot be easily dismissed. To paraphrase Karl Popper, hypotheses survive by not being falsified.

Thus in the absence of clinical trials which provide strong and consistent evidence regarding a protocol for the prevention or reversal of subclinical atherosclerosis, there seems little alternative, aside from addressing the factors discussed above, than to obtain guidance from observational studies that, in the context of primary prevention, have provided impressive reductions in the risk of both heart disease and diabetes through lifestyle and dietary pattern choices. While these studies involved overt diabetes or CHD event endpoints, the long follow-up times involved and the very large risk reductions suggest that part of the impact may have been on subclinical atherosclerosis [52–55].

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The evidence falsifying the hypothesis that LDL drives atherosclerosis has been largely ignored. It is suggested that considerable benefit might derive from recognizing that there is a problem and initiating research aimed at providing an evidence base for interventions that directly focus on silent atherosclerosis. It would also appear that considerable clarity could be introduced into the interpretation of studies of primary prevention of CHD by considering results in the context of the prevalence and progression of atherosclerosis rather than focusing on adverse coronary events.

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