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Which lipid fraction is the target and how often should this be monitored?

Gilbert Thompson

“Without cholesterol there can be no atherosclerosis” stated Anitchkov in 1915 and the causal role of lipids in this ubiquitous disorder is now indisputable. The likelihood of developing its cardiovascular consequences, especially coronary heart disease (CHD), is enhanced by dyslipidaemia, which manifests itself either as an increase in low-density lipoprotein (LDL), resulting in hypercholesterolaemia, or in very-low-density lipoprotein (VLDL), resulting in either hypertriglyceridaemia or, if VLDL remnants accumulate, mixed hyperlipidaemia. In contrast, high-density lipoprotein (HDL) is usually decreased, especially when triglycerides are raised.

The concept of ‘risk factors’, inherent or acquired traits that increase the likelihood that the bearer will develop CHD, originated in Framingham. The prospective study which started there in 1948 measured a range of putative risk factors in a representative sample of adults who were then followed up to determine which of them developed CHD. The role of lipids was established by Kannel et al, who demonstrated correlations between the concentrations of serum cholesterol and the major lipoprotein classes at entry to the study and the development of CHD during the subsequent 14 years. The incidence of CHD during follow-up was found to be threefold greater in subjects with serum cholesterol and VLDL and LDL concentrations in the top versus the bottom quartile, but apart from a raised VLDL in postmenopausal women, measurement of lipoprotein fractions was no more predictive than serum cholesterol alone. The main exception was HDL cholesterol, which was shown in a subsequent analysis of Framingham data to correlate even more strongly than LDL cholesterol with risk of CHD, but inversely.

LIPIDS, LIPOPROTEINS AND THEIR RATIOS AS RISK FACTORS

The opposite effects on risk of LDL and VLDL, on the one hand, and HDL, on the other, has resulted in the use of the ratios of their lipid or lipoprotein components as a means of predicting cardiovascular morbidity and mortality. These ratios include total:HDL cholesterol, LDL:HDL cholesterol and, latterly, apolipoprotein B:apolipoprotein A-1 (apoB:apoA-1). The increasing prevalence of obesity and the metabolic syndrome has led to the use also of non-HDL cholesterol as an index of risk and a therapeutic target, in that this variable includes LDL cholesterol and also VLDL and remnant cholesterol, both of which are increased by the hypertriglyceridaemia which is a common accompaniment of those conditions.

The relative predictive power of these various criteria of lipid-associated risk has been evaluated in numerous studies. In the Framingham Study, LDL cholesterol predicted CHD events marginally better than total cholesterol but the total:HDL cholesterol ratio was better than both. Later data from Framingham confirmed this and found that the total:HDL cholesterol, LDL:HDL cholesterol and apoB:apoA-1 ratios were all comparable in this respect, although in a recent, large case–control study the apoB:apoA-1 ratio was more informative than the cholesterol ratios. An analysis of 19 trials, in which non-HDL cholesterol was compared with LDL cholesterol or apoB in predicting hard cardiovascular events in almost 75 000 subjects, found that non-HDL cholesterol was better in 14, equivalent in four and worse in only one trial. However, in the Prospective Studies Collaboration, which analysed 55 000 vascular deaths, the total: HDL cholesterol ratio was twice as strong a predictor of coronary mortality as LDL cholesterol and 40% stronger than non-HDL cholesterol, as well as being a weak predictor of stroke mortality in people aged <70.

Several recent studies have examined the predictive power of lipids for cardiovascular outcome in patients receiving lipid-modifying treatment. A post hoc analysis of two statin trials in almost 19 000 patients (‘Treating to New Targets’ and ‘Incremental Decrease in End points through Aggressive Lipid lowering’) showed that total:HDL cholesterol and apoB:apoA-1 ratios correlated with cardiovascular events more strongly than did LDL cholesterol, whereas in statin-treated post-coronary syndrome patients these three indices and non-HDL cholesterol were all equally predictive.

A recent meta-analysis of lipid-modifying treatment trials, more than half of them involving statins, concluded that reductions in cardiovascular events were strongly correlated with decreases in LDL cholesterol but, unexpectedly, not with increases in HDL cholesterol, possibly because statins have a relatively weak HDL-raising effect. However, other studies have found the opposite, with the level of HDL cholesterol on treatment being an important determinant of outcome, especially when pretreatment levels were low. Overall, the data reviewed here suggest that the best predictor of cardiovascular outcome in both treated and untreated subjects is the ratio of pro-to-atherogenic lipoproteins, expressed either as total:HDL cholesterol or as apoB:apoA-1.

LIPID CRITERIA USED IN CURRENT GUIDELINES

The criteria of risk advocated in current guidelines differ according to which side of the Atlantic they emanate from. In the USA, the third report (Adult Treatment Panel III) of the National Cholesterol Education Program (NCEP) uses LDL cholesterol as the determinant of treatment initiation and as the therapeutic goal in various categories of CHD risk, with non-HDL cholesterol as an alternative goal in hypertriglyceridaemic subjects. Risk is estimated using a Framingham-based point system, which includes HDL cholesterol and non-lipid risk factors. The NCEP emphasis on LDL probably reflects the fact that the scientific evidence for its causal role in atherosclerosis is stronger than it is for HDL.

The fourth Joint European Societies Guidelines estimate risk of fatal cardiovascular events using the Systematic Coronary Risk Evaluation (SCORE) system. This uses similar criteria to Framingham to calculate risk but differs from the NCEP guidelines in prioritising the total:HDL cholesterol ratio rather than LDL cholesterol. In Britain the second set...
of guidelines of the Joint British Societies (JBS 2) estimate total cardiovascular risk also using Framingham-type criteria and the total: HDL cholesterol ratio, although they define an LDL cholesterol level of <2 mmol/l as a treatment target.  

VARIABILITY AND FREQUENCY OF LIPID MEASUREMENTS

In an accompanying article in this issue of the journal Takahashi et al (see page 448) deal with the question as to which of the various lipid risk factors provides the best estimate of true change in the long term (‘signal’) and the least within-person variability in the short term (‘noise’), the latter reflecting both biological and analytical variation. Data were obtained from more than 15 000 healthy Japanese subjects not receiving lipid-modifying treatment who underwent annual lipid measurements over a 4-year period. The results show that the signal-to-noise ratio at 3 years was higher for total: HDL cholesterol and LDL: HDL cholesterol ratios than for total, LDL and HDL cholesterol. These data provide further support for the use of ratios rather than concentrations of single lipids as criteria of cardiovascular risk. They also suggest that the validity of changes observed on re-screening of untreated subjects would be enhanced if this was performed every 3 years rather than annually. Similar conclusions about the frequency of measuring lipids were reached by Glasziou et al after analysing data from statin-treated subjects. However, concerns about compliance may take precedence over the variability concern among clinicians, many of whom will prefer to measure lipids annually in patients receiving long-term drug treatment once they have achieved the desired target levels.

CONCLUSIONS

The conceptual appeal of the total: HDL cholesterol ratio as an index of lipid-associated cardiovascular risk is supported both by its superior predictive power compared with total, LDL or HDL cholesterol and by its lower within-person variability. However, none of the current guidelines specify what constitutes a desirable total: HDL cholesterol ratio, although JBS 2 defines ≥6 as indicative of high risk. Data from the PROCAM study showed that the incidence of CHD remained relatively low in men with ratios between 2 and 4 but then rose exponentially, whereas cardiovascular mortality doubled in the Prospective Studies Collaboration when the ratio increased from 4 to 5. Extrapolation of these results to clinical practice suggests that in dyslipidaemic subjects lipid-modifying treatment should be aimed at reducing the total: HDL cholesterol ratio to <4. The nature of the measures needed to achieve this target will depend on whether an elevated ratio reflects increased proatherogenic or decreased anti-atherogenic lipoproteins or both; in the last case, combination treatment may be required.

Looking to the future, the increasing availability of apoB and A-1 assays may eventually result in these apolipoproteins replacing LDL and HDL cholesterol as risk markers. If so, the apoB: A-1 ratio could become the preferred criterion of lipid-associated risk, as suggested by a recent analysis of the INTERHEART study which showed it to be a significantly better predictor of myocardial infarction than any of the cholesterol ratios.

Competing interests None.

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