

Is Apolipoprotein B and Small, Dense low density lipoprotein a better marker of cardiovascular risk?

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Abstract

The association between low density lipoprotein cholesterol and cardiovascular risk is well established. However, the measurement of the cholesterol content of this lipoprotein incompletely accounts for the risk of cardiovascular disease. As part of its limitations, LDL cholesterol concentration does not precisely count the number of LDL particles, but Apo B does. The levels of Apolipoprotein B and small dense low density lipoprotein have been shown to be associated with risk of cardiovascular disease. There is one Apo B per LDL particle; hence, LDL-Apo B accurately defines LDL particle number. Also, the ratio of cholesterol to Apo B differs from person to person, thereby explaining why LDL-cholesterol level does not necessarily indicate LDL particle number. Furthermore, Apo B reflects the concentration of potentially atherogenic particles i.e. the total Apo B level is a measure of the total number of lipoprotein particles in LDL, IDL and VLDL (non-HDL cholesterol). This implies that if most Apo B-containing lipoproteins in each fraction are atherogenic, the total concentration of Apo B will indicate cardiovascular risk better than LDL cholesterol level does. A predominance of small, dense, low-density lipoprotein cholesterol particles has been associated with a 3-fold or even greater risk of coronary heart disease in a collection of cross-sectional studies. Recent prospective evidence describes small, dense, low-density lipoprotein cholesterol as predictive of coronary heart disease as most of the traditional risk factors like smoking and elevated blood pressure. Cardiovascular risk is more directly related to the number and sizes of circulating atherogenic particles than to the concentration of cholesterol in these particles; therefore, adopting the traditional lipid profile (Triglyceride, HDL, LDL, total cholesterol etc.) will result in an underestimation of the true atherogenic burden as well as serve as a poor assessment of cardiovascular risk in individuals

Keywords: Cardiovascular diseases, Low density lipoprotein, Apolipoprotein B, Small dense low density lipoprotein, high density lipoprotein, triglycerides, total cholesterol

1. Introduction

1.1 Burden of cardiovascular diseases

Cardiovascular diseases (CVD) remain leading causes of mortality and morbidity in developed countries and are steadily emerging as a major public health problem in developing countries. The increasing burden of cardiovascular diseases in developing countries has generated concern in recent years. For the better part of the last century, cardiovascular diseases were associated with industrialized and developed countries. However, since the turn of the century, the absolute burden of cardiovascular diseases has been greater in developing countries [1][2].

The Global Burden of Diseases study (2010) associated 66.7% of deaths worldwide with non-communicable diseases, with cardiovascular diseases being responsible for 43% of the deaths. In spite of the total increase in CVD burden, effective preventive and therapeutic burden has led to a decline in the mortality and morbidity associated with cardiovascular diseases in developed countries [4].

In developing countries, on the other hand, the increasing burden of cardiovascular diseases has been identified and attributed to an increase in the prevalence of risk factors triggered by industrialization, rural-urban population drift, urbanization, lack of access to modern medical

intervention etc. [5-8]. However, most of the risk factors can be prevented and chronic conditions managed via modified lifestyles. These risk factors include smoking, sedentary lifestyles, inappropriate dietary habits, glucose intolerance, hypertension, dyslipidemia and obesity.

2. Role of traditional lipid profile in the assessment of cardiovascular risk

Dyslipidemia, alongside with elevated blood pressure/hypertension, abdominal obesity and glucose intolerance/diabetes mellitus, is a component of metabolic syndrome and has been established as a risk factor for cardiovascular disease [9][10]. Other risk factors associated with cardiovascular disease include sedentary lifestyle, male gender, older age, excessive alcohol consumption, smoking as well as family history of cardiovascular diseases [11-15].

Measurement of lipid profile is the most common approach devised in assessing and identifying individuals at risk of cardiovascular diseases [16]. Current clinical guidelines emphasize the estimation of the indices of traditional lipid profile (Total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) in the assessment of cardiovascular risk.

Several studies have revealed an inverse relationship between risk of cardiovascular diseases and plasma high density lipoprotein (HDL) levels [17-20]. Other studies have demonstrated a positive correlation between elevated concentrations of total and/or low density lipoprotein cholesterol levels and cardiovascular risk [21-23].

Also, increases in HDL cholesterol alone have also been established to be insufficient in reducing the risk of cardiovascular events [24], thereby implicating serum triglycerides and LDL cholesterol as well as other elements such as Apolipoprotein B levels in the assessment of cardiovascular risk [25].

3. Role of Apolipoprotein B and Small, Dense low density lipoprotein in the assessment of cardiovascular risk

Not only is the present traditional lipid profile approach complex, rather, other indices have been suggested to be better markers in the assessment of cardiovascular risk. The best studied and established of these is the measurement of apolipoprotein B and small, dense low density lipoprotein. Considerable evidence from studies have shown in different clinical scenarios and analytical reasons why ApoB and small, dense LDL may have a

greater utility in cardiovascular disease risk assessment.

Apolipoprotein B-100 and small, dense LDL are beneficial markers of cardiovascular disease. Apo B-100 demonstrates the number of LDL particles reflecting atherogenicity better than the LDL cholesterol concentration. On the other hand, small, dense LDL is a lipoprotein subclass that causes atherosclerosis with a much higher risk than large LDL. The results of both apoB-100 or small, dense LDL can be good risk markers of cardiovascular diseases when tested individually, whereas the cause of cardiovascular diseases can be better explained by analyzing them in combination [26].

Firstly, the traditional lipid profile (basically, LDL cholesterol), does not account for all the cardiovascular risk associated with dyslipidemia as a risk factor. As part of its limitations, LDL cholesterol concentration does not precisely count the number of LDL particles, but Apo B does. There is one Apo B per LDL particle; hence, LDL-Apo B accurately defines LDL particle number. Also, the ratio of cholesterol to Apo B differs from person to person, thereby explaining why LDL-cholesterol level does not necessarily indicate LDL particle number [27].

Furthermore, Apo B reflects the concentration of potentially atherogenic particles [28] i.e. the total Apo B level is a measure of the total number of lipoprotein particles in LDL, IDL and VLDL (non-HDL cholesterol). This implies that if most Apo B-containing lipoproteins in each fraction are atherogenic, the total concentration of Apo B will indicate cardiovascular risk better than LDL cholesterol level does [29]. Also, several studies have revealed that the total cholesterol content of non-HDL cholesterol correlates strongly with total Apo B levels [27][30], with several investigators also suggesting that non-HDL cholesterol better represents atherogenic cholesterol than LDL cholesterol[27][30][31].

Apo B, which is present in VLDL, IDL, large buoyant LDL and small, dense LDL, reflects the total number of atherogenic particles [32], i.e. the total number of ApoB-containing lipoprotein particles [33]. Elevated Apo B levels may indicate an increased number of small, dense LDL particles which are prone to oxidation, promote inflammatory responses as well as plaque formation [34].

Furthermore, measurement of Apo B concentration comes with an advantage- the concentration of apolipoproteins do not change after meals, neither do they change during different times of the day. This remains an advantage in comparison

with the traditional lipid profile which is best estimated while the subjects are observing a 10-14 hour fast. Another advantage of estimating Apolipoprotein levels is that they are better markers, when compared to traditional lipid measures, of coronary heart disease risk in patients taking lipid-lowering treatment.

On the other hand, the published data hasn't been totally consistent as some other studies have revealed that ApoB and Apo A-1 did not perform better, when compared with traditional lipid profile, thereby triggering a debate [35-40]. The global INTERHEART study of risk factors for acute myocardial infarction in 52 countries however concluded that 'the Apo B/A-1 ratio was the most important risk factor for all geographic regions'.

Low density lipoproteins comprises heterogeneous particles characterized by varying sizes, chemical compositions, densities, physiologic properties and atherogenic properties i.e. all LDL are not created equally. Large buoyant LDL represents the good LDL responsible for the transport of cholesterol to peripheral tissues for cell membrane maintenance, bile acid synthesis by the liver and for the production of steroidal hormones.

Small dense LDL is a component of the lipid triad associated with atherogenic dyslipidemia and has been demonstrated in several clinical studies to be an independent risk factor for cardiovascular disease [41]. Also, the Small Dense Low Density Lipoprotein cholesterol: low density lipoprotein cholesterol ratio plays a vital role in the determination of cardiovascular risk [42].

A predominance of small, dense, low-density lipoprotein cholesterol particles has been associated with a 3-fold or even greater risk of coronary heart disease in a collection of cross-sectional studies, even at 'normal' concentrations of LDL cholesterol [43][44]. Furthermore, the QUEBEC cardiovascular study demonstrated the association between coronary heart disease and a prevalence of small, dense LDL in the first seven years of its follow-up [45].

Recent prospective evidence describes small, dense, low-density lipoprotein cholesterol as predictive of coronary heart disease as most of the traditional risk factors like smoking and elevated blood pressure [46][47]. Koba *et al*[48] (2006), on the other hand, specified that a progression of coronary heart disease was associated with the concentration of small, dense LDL and not the size of the LDL particles.

There are several credible biochemical mechanisms implicating small dense low density

lipoprotein cholesterol to be more potentially atherogenic compared to its larger, buoyant and lighter counterparts [49]. Studies have shown small dense LDL particles to be more atherogenic than large buoyant particles, as they are more susceptible to oxidation and have a decreased affinity for LDL receptor [50].

In conclusion, cardiovascular risk is more directly related to the number and sizes of circulating atherogenic particles than to the concentration of cholesterol in these particles [51][52]. Therefore, adopting the traditional lipid profile (Triglyceride, HDL, LDL, total cholesterol etc.) will result in an underestimation of the true atherogenic burden [52] as well as serve as a poor assessment of cardiovascular risk in individuals. However, the question related to the better marker in the assessment of cardiovascular risk remains unanswered.

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