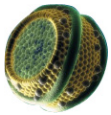
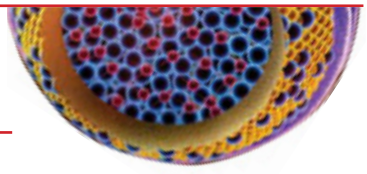
THE PATHCARE NEWS



Apolipoprotein B & A1



WHY SHOULD WE MEASURE APO B & APO A1?

The association between cardiovascular disease (CVD) risk and plasma low density lipoprotein-cholesterol (LDL-c) levels is indisputable. Accordingly, all screening and therapeutic guidelines are based on total cholesterol (TC) or LDL-c levels. However, focusing only on LDL-c, has several limitations:

- Many patients with atherosclerotic disease have normal LDL-c levels.[1]
- Significant risk for CVD often persists, despite achieving LDL-c goal with treatment.[2]
- In certain dyslipidaemias with high CVD risk, other atherogenic lipoproteins predominate - such as very low density lipoprotein (VLDL) remnants, chylomicron (CM) remnants and intermediate density lipoprotein (IDL).[3]

CVD risk appears to be more directly related to the number of circulating atherogenic particles that contact and enter the arterial wall, than the amount of cholesterol in these lipoproteins.[4,5]
Experimental studies indicated that Apolipoprotein B (ApoB) is instrumental in the initiation of atherosclerosis.[2] Subendothelial retention of ApoB-containing particles takes place through a gradient-driven process, with an increased rate of diffusion when the concentration of circulating lipoprotein particles is raised.[6]

Due to the technical difficulty of measuring lipoprotein particles directly, the cholesterol carried within the lipoprotein particles has been used as a surrogate marker for the concentration of these lipoproteins.[7] Unfortunately, since the cholesterol content of atherogenic lipoprotein particles may vary considerably, the cholesterol levels may not reflect lipoprotein particle levels accurately. LDL-c underestimates the number of LDL particles in individuals with predominantly cholesterol depleted small dense LDL (sd-LDL) particles, typically seen in the metabolic syndrome and Type 2 Diabetes Mellitus (DM).[2] Ironically, these lipoprotein particles are the most atherogenic!

In contrast, each potentially atherogenic lipoprotein particle contains only one ApoB molecule and measurement of ApoB therefore reflects the number of atherogenic particles. (Fig 1) Indeed, recent evidence indicates that ApoB provides a more accurate estimate of CVD risk than LDL-c.[5]

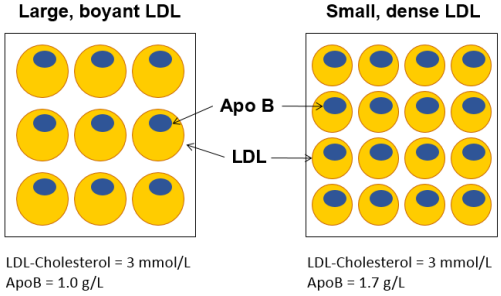


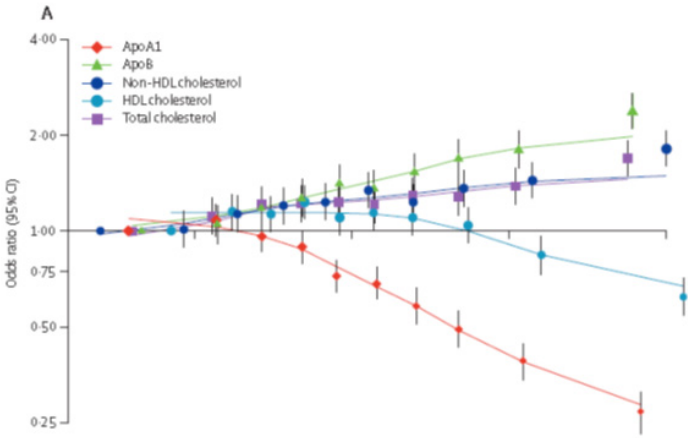
Figure 1

WHAT DO WE MEASURE?

The ApoB assay measures both Apo B100 (the structural protein of LDL, VLDL, IDL and lipoprotein(a)) and Apo B48 (which forms part of CM and CM remnants).

However, even post prandially, there are so few Apo B48 particles compared to the number of Apo B100 particles, that for all practical purposes, measured ApoB represents Apo B100.[5] Furthermore, most of the plasma ApoB is carried in LDL particles, as VLDL particles are much larger and relatively few in number.[2] In most instances, more than 90% of total plasma ApoB is associated with LDL. Therefore, the ApoB level is a good indication of LDL concentration.[5]

Apolipoprotein A1 (ApoA1) is the major structural protein of high density lipoprotein (HDL) particles and reflects the atheroprotective side of lipid metabolism. ApoA1 is probably the most useful in conjunction with ApoB in assessing the balance between atherogenic and atheroprotective cholesterol transport, as determined by the ApoB:ApoA1 ratio.[8] Studies have demonstrated the superiority of the ApoB:ApoA1 ratio to any of the cholesterol ratios in the estimation of the risk for acute myocardial infarction (MI) in all ethnic groups, in both sexes, and at all ages. (Fig 2)[9]



Risk of myocardial infarction for increasing decile medians (adjusted for age, sex and region) of lipids, lipoproteins and apolipoproteins.[9]

Figure 2

USE OF APOB IN HYPERTRIGLYCERIDAEMIA

The larger Triglyceride(TG)-rich particles, such as CM and large VLDL are generally not atherogenic, whereas CM remnants and VLDL remnants (IDL) are.[10] In patients with hypertriglyceridaemia, high ApoB levels indicate the presence of potentially atherogenic lipoproteins such as sd-LDL, or smaller TG-rich particles, such as VLDL remnants.

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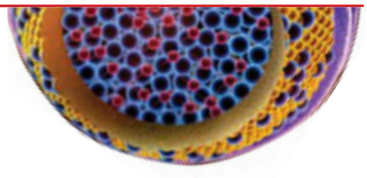


Low ApoB levels would indicate an increase in larger TG-rich lipoproteins, such as CM and larger VLDL, which are less atherogenic.[2]
The atherogenic dyslipidaemia associated with Type 2 DM & metabolic syndrome is characterised by high TG, sd-LDL and low HDL-c. The LDL-c typically underestimates risk in these patients, whereas raised ApoB correctly reflects the increase in sd-LDL.[2]

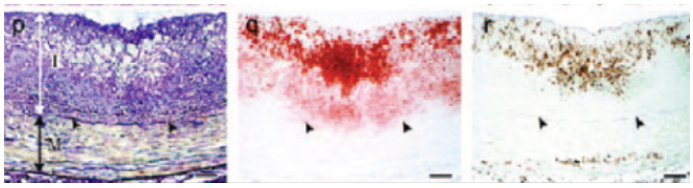
In Familial Combined Hyperlipidaemia (FCH), one of the most common familial forms of hyperlipidaemia, the typical lipid phenotype of raised TC and TG, and low HDL-c may vary substantially within an individual over time. However, ApoB levels and sd-LDL are consistently increased, making ApoB a valuable tool in the evaluation and diagnosis of FCH.[11]

However, in certain genetic syndromes with hypertriglyceridaemia, there may be a risk for CVD, without raised ApoB levels. Dysbetalipoproteinaemia (Familial Type III dyslipidaemia) is highly atherogenic, but ApoB levels are low to normal. This is due to the accumulation of cholesterol-rich VLDL remnant particles.[12] Dysbetalipoproteinaemia may be suspected when both the TC and TG concentrations are increased, in in a 2:1 ratio, with a significant difference between measured and calculated LDL-c. Screening for dysbetalipoproteinaemia with an ApoB:TC ratio of <0.15, has also been proposed.[13] In these patients, Non-HDL-c is a better marker for CVD risk than ApoB.

USE OF APOB IN HYPERCHOLESTEROLAEMIA:

ApoB adds important information in patients with moderate hypercholesterolaemia.[14] It has been found that ApoB improves the ability to discriminate incident CVD cases in patients with high LDL-c. Among patients with high LDL-c, those with high ApoB were at increased risk for MI compared with those with low ApoB.[15,8]

In severe hypercholesterolaemia, however, such as in Familial Hypercholesterolaemia, ApoB will inevitably be raised and therefore contributes no additional information.[14]



USE IN TREATMENT:

Statins lower LDL-c and Non-HDL-c more than ApoB; therefore many patients who achieve their LDL-c and Non-HDL-c goals still have raised ApoB. This may explain why these patients remain at risk.[2] ApoB would therefore provide a more reliable goal for lipid-lowering treatment, as well as a better assessment of residual risk.

ApoB treatment targets for patients at high and very high total CVD risk, are <1.0 g/L and <0.8 g/L, respectively.[16]

PRACTICAL:

Fasting is not required for ApoB measurement.
In contrast to LDL-c, ApoB measurement is not affected by high TG in the blood sample.

SUMMARY:

- Unlike LDL-c, ApoB is not affected by the varying amounts of cholesterol content in atherogenic lipoprotein particles, therefore it provides a better index of CVD risk than LDL-c.
- ApoB also serves as a more reliable guide to the adequacy of lipid-lowering treatment.
- In a rapidly growing subset of the population with obesity, metabolic syndrome and diabetes, ApoB compensates for the limitations of LDL-c in the assessment of CVD risk.
- Valuable additional information is obtained by measurement of ApoB in patients with hypertriglyceridaemia and moderate hypercholesterolaemia, thereby providing a refined risk assessment.
- However, certain genetic syndromes with hypertriglyceridaemia may be associated with high risk for CVD, without raised ApoB levels.

Compiled by dr Esmé Hitchcock, Chemical Pathologist.

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