Measured LDL – an unnecessary expense or a customer service?

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This article briefly describes our experience arising from the New Zealand national cardiovascular disease (CVD) and diabetes screening programmes which evaluates a patient's risk factors and probability of a CVD event over 5 years (1). For high risk individuals identified by the programmes, intensive lifestyle changes are recommended, supplemented by drug interventions for blood pressure lowering, diabetes control and lipid modification with regular follow up assessments. The programmes have increased early morning attendances for fasting blood tests leading to increased waiting times, patient dissatisfaction and stressed phlebotomists. Government targets are to have a five year risk prediction for 95% of the eligible population within the next two years so these pressures will continue. Screening for diabetes now utilises HbA1c for which fasting is not required.

But fasting is still a requirement for lipids under New Zealand guidelines, though a non-fasting sample for total cholesterol (TC) / high density lipoprotein cholesterol (HDL) ratio is acceptable for CVD risk assessment (2). Internationally, the Emerging Risk Factors Collaboration confirmed that non-fasting lipid measurements are acceptable for CVD risk screening (3) and, based on this evidence, some of our local Practitioners have already adopted non-fasting lipids for CVD screening. These developments have helped reduce the early morning pressures. However, our data show that 35% of all community-generated biochemistry requests have a lipid profile requested and >40% of these lipid requests still require fasting. This likely reflects the monitoring of lipid modification (Statin therapy) by estimation of low density lipoprotein cholesterol (LDL).

In New Zealand LDL is estimated by calculation using the Friedewald formula (4). This formula allows calculation of the contribution of very low density lipoprotein cholesterol (VLDL) to serum TC (LDL = TC - HDL - triglyceride / 2.22) with triglyceride / 2.22 as proxy for the estimation of VLDL. The current national guidelines state that a fasting sample is mandatory due to effect of food intake on the triglyceride which causes the equation to ‘overestimate’ VLDL and, therefore, artefactually ‘underestimate’ LDL. Internationally, measured LDL methods (LDLm) were introduced to overcome this shortcoming (5) and we decided to investigate whether this approach could further reduce the need for patient fasting.

We used the 2nd generation Roche LDL-C plus method running on a Cobas 6000 analyser. The method principle is a homogenous enzymatic cholesterol assay (cholesterol esterase, cholesterol oxidase / peroxidase coupling reaction) modified by the addition of a non-ionic detergent, a sugar compound and magnesium which enables the selective determination of LDL (6). The method is standardised against the reference beta quantification method and Roche data indicates little interference from high levels of VLDL, chylomicrons and triglyceride. We calculated LDL (LDLc) by the Friedewald equation using Roche TC, HDL and triglyceride reagents on the same analyser. Application parameters and calibrations were as per the manufacturer’s recommendations. Samples were freshly drawn lithium–heparin plasma and fasting status determined by direct questioning of the patients.

Data on 543 samples (243 fasting, 300 non-fasting) is summarised in Figure 1. The difference between the two LDL methods (LDLc minus LDLm) is plotted against the triglyceride in the same sample. It can be seen that at lower triglyceride levels the LDLm has a negative bias compared to LDLc but at triglyceride levels >2.5mmol/L the LDLc has an increasing negative bias to LDLm. Plotting fasting and non-fasting data separately revealed exactly the same “tip over” point (2.5mmol/L).

![Figure 1. Triglyceride (mmol/L) v (LDLc minus LDLm) n=543](image-url)
Comparing all samples with triglyceride <2.5mmol/L showed a strong correlation between the two methods (Figure 2). Our data supports the conclusions of van Deventer et al, who compared LDLC and multiple LDLm assays with reference methods (6). They also found lower LDLm levels compared to LDLC in fasting samples but found LDLC more accurate compared to reference methods. With raised triglyceride, LDLc became negative compared to LDLm which was also closer to the reference method target. Their “tip over” point was a triglyceride of 2.3mmol/L.

We conclude that it is the triglyceride level that differentiates, not fasting status, and we conclude it is necessary to estimate LDLm only on patients whose triglyceride levels are >2.5mmol/L (fasting or non-fasting). This was achieved by programming an appropriate rule in our computer middleware (IT3000, Roche Diagnostics). If triglyceride ≥2.5 mmol/L, LDLm is automatically added to the lipid profile, the LDLc result nullified and an appropriate interpretive comment added. This rule operates reflexively – the sample is re-sampled for a LDLm assay before the sample rack leaves the analyser. No operator input is required and auto-validation completes the reporting. By combining the two methods in this way we are able to give more consistency to our LDL results and target LDLm to where it is most effective. The reflex rule approach also minimises extra reagent costs which has been an impediment to the use of LDLm in NZ.

In Kaitaia our data indicate an LDLm added to 18% of lipid requests, though this may vary in other communities. Current reagent, calibration and QC costs approximates to an extra $1 per reportable sample. Obviously, for larger laboratories this could be a significant reagent cost increase, but this should be set against the appreciable benefits, for the laboratory and the wider local community. For doctors, it allows patients to be referred to the laboratory straight from the health centre thus improving result turn-around-time. For patients, it eliminates the need for overnight fasting which many find onerous, particularly if repeated for therapy monitoring. It gives flexibility of attendance and, there is no need for patients to return home from the GP surgery to fast overnight and return for a blood test – a problem for remote communities. For the laboratory, it removes uncertainty about sample validity and assures accurate LDL results regardless of patient fasting status or diagnosis. The net effect would be to reduce early morning phlebotomy queuing, reduce patient waiting times, increase customer satisfaction and encourage patient compliance with the screening programmes.

In Kaitaia, our patient attendance time profiles have changed in the last year with our peak now at 10.30 – 11.00am with more patients attending after 2pm. Complete elimination of the need for fasting would continue this process but given the demonstrated bias between LDLm and LDLC an amendment to the national guidelines regarding the exact role of LDLm may be required to achieve this aim.

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\text{Figure 2. } \text{LDLm } \oplus \text{LDLc (Triglycerides <2.5mmol/L) } (n = 300) \\
\text{y = 0.9445x - 0.0234} \quad R^2 = 0.9988
\]
The current practice of laboratories reporting inaccurate LDLc results in samples with raised triglyceride should also be reviewed. In summary, LDLm is an opportunity for New Zealand laboratories to manage their phlebotomy services better and also contribute cost effectively to the well being of their local population by encouraging compliance with the national CVD screening programme. Targeted LDLm should be considered for wider application in New Zealand.

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References

Correction
In the November 2012 issue the abstracts of the Annual Scientific Meeting of the NZIMLS were published. Unfortunately the name of a second author was omitted from one of the abstracts (page: 90). Below is the corrected abstract.

The emerging roles of medical scientists in humanitarian assistance operations
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There is a growing demand for medical scientists (MSs) to provide pathology services on short notice to high risk operating environments. Recent major humanitarian aid (HA) operations including the Rwanda genocide, the Indian Ocean tsunami and the Haiti earthquake have identified that the delivery of pathology services remains to be challenging. High risk areas such as Afghanistan, Colombia, Somalia and the Darfur region of Sudan that pay little attention to humanitarian law and principles pose extra stress to HA providers. Additionally, the operational uncertainty makes planning and forecast difficult and it is likely that each affected population will have a different demographic profile for treatment. The MSs required to support task-specific land-based operations in complex terrain must learn new skills to meet these emerging challenges. The further development of standards, accountability and training requirements should enhance their overall delivery efficiency. The provision of specialised pathology support on HA operations is dependent upon many new factors. Firstly, they must possess communication skills enabling them to work more effectively together, both interculturally and interprofessionally, so that critical decisions can be made more quickly. Secondly, performance of mission-specific tasks must include operational flexibility and multitasking considerations in support of wider interests. Thirdly, survivability and mobility must be improved, so that the MSs can operate with better preparation to sustain prolonged operations. This paper will highlight several challenges that the MSs are likely to encounter. The information will enable future MSs to maintain a competitive advantage when selected for deployment.