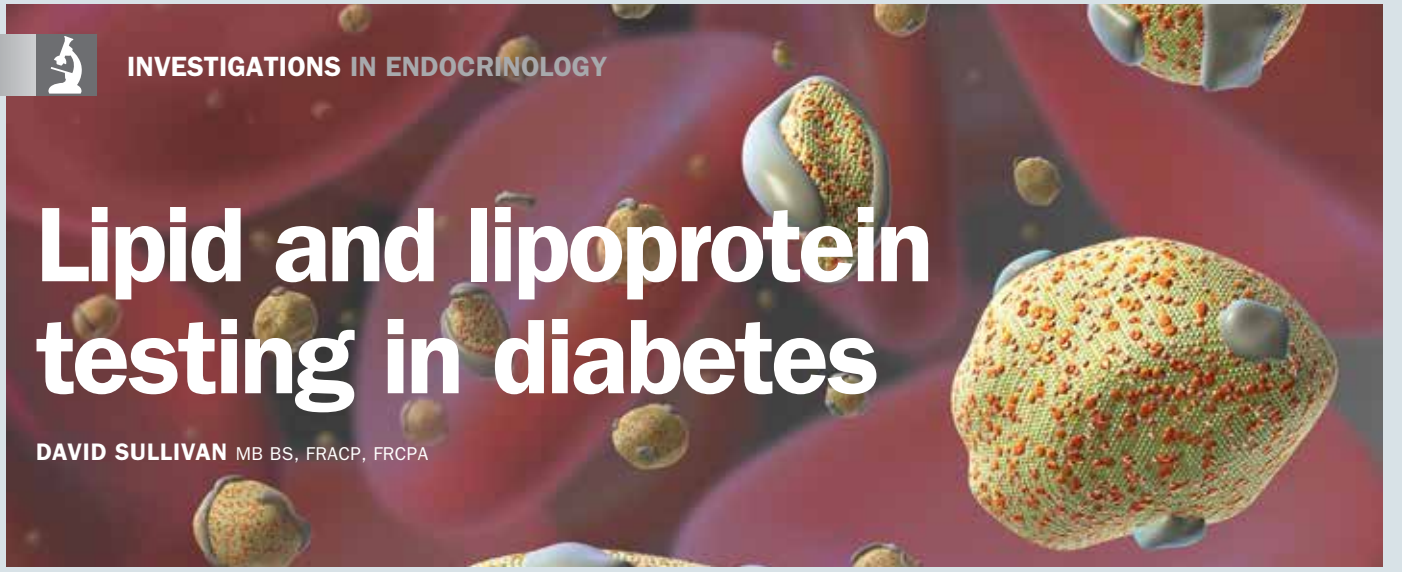

Lipid and lipoprotein testing in diabetes

DAVID SULLIVAN MB BS, FRACP, FRCPA

This section uses case scenarios to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.

Plasma lipid and lipoprotein levels affect an individual's risk of serious cardiovascular disease (CVD) events and acute pancreatitis. Endocrinologists, primary care physicians and health professionals who specialise in diabetes now require a greater level of sophistication in their understanding of lipid and lipoprotein tests. Guidelines concerning utilisation and interpretation of these tests continue to evolve.[1-5]

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Associate Professor Sullivan is Senior Staff Specialist in the Department of Chemical Pathology at Royal Prince Alfred Hospital, Sydney; and Clinical Associate Professor, NHMRC Clinical Trials Centre, Sydney Medical School, The University of Sydney, Sydney, NSW.
SERIES EDITOR: Dr Bernard Champion BEc, MB BS, BSc(Med)(Hon 1), FRACP, MMedEd is a Lecturer at Sydney Medical School Nepean and The University of Sydney; and Head of Department, Endocrinology and Diabetes, Nepean Blue Mountains Local Health District, Penrith, NSW.

Case 1. **Mr PT is a 66-year-old man with type 2 diabetes of eight years' duration. He undertook a routine lipid test and now informs you that because he was in a rush on the day he attended the blood collection he forgot to fast. The results include: total cholesterol, 6.9 mmol/L; triglycerides, 3.4 mmol/L; and HDL-cholesterol (HDL-C), 1.1 mmol/L.**

Can any useful information be derived from this nonfasting set of results regarding diagnosis of hyperlipidaemia and assessment of CVD risk?

Mr PT's total cholesterol level is elevated, but failure to fast rarely affects total cholesterol level to any great degree. Consequently, the cholesterol level is likely to remain elevated if these tests are repeated in the fasting state. His triglyceride level is also elevated, suggesting a mixture of hypercholesterolaemia and hypertriglyceridaemia. As the latter may reflect recent food intake, a 12-hour fast would be required to standardise the measurement of plasma triglycerides and hence determine whether or not hypertriglyceridaemia is present. This is an important issue because type 2 diabetes is often associated with hypertriglyceridaemia, sometimes in combination with hypercholesterolaemia.

The mere fact that Mr PT's nonfasting triglyceride level is elevated indicates an increased risk of CVD.[6] In this regard, food intake may represent a 'stress test' for lipoprotein metabolism, thereby increasing the sensitivity of the triglyceride level as a risk factor. Of course the variability of food intake interferes with the standardisation of the measurements, so the results should only be interpreted semiquantitatively. The evidence suggests that samples collected approximately four hours after food intake are particularly indicative of CVD risk.[6]

Mr PT's nonfasting lipid results can contribute to assessment of CVD risk in other ways. His total cholesterol and HDL-C levels can provide the necessary lipid and lipoprotein components for the estimation of absolute risk using the National Vascular Disease Prevention Alliance (NVDPA) Australian CVD risk calculator.[2] On the other hand, the absence of a fasting triglyceride result precludes the use of the Friedewald equation to estimate LDL-cholesterol level (LDL-C = total cholesterol – HDL-C – [fasting triglycerides/2.2] where concentrations are in mmol/L). As an alternative, direct measurement of the LDL-C level could be performed on a nonfasting sample, but this may not be as efficient or reliable. More importantly, there is increasing enthusiasm for the use of the non-HDL-C level (non-HDL-C; total cholesterol – HDL-C) as an alternative; this can be derived using the results from nonfasting samples. It will be appreciated that the small change in HDL-C level that follows food intake will have little effect on the final non-HDL-C result. Also, there is increasing evidence to suggest that non-HDL-C levels provide more accurate estimation of CVD risk than LDL-C levels.[7,8] This is true for both prediction of CVD risk and assessment of response to treatment.

The superiority of non-HDL-C over LDL-C levels can be explained by the fact that elevated triglyceride levels promote changes in the composition of cholesterol-rich lipoproteins such as LDL and HDL. The action of cholesteryl ester transfer protein (CETP) leads

Practice points

- Elevated nonfasting triglyceride levels are indicative of increased CVD risk.
- Nonfasting total cholesterol and HDL-C levels can be used to calculate absolute CVD risk and non-HDL-C level. Non-HDL-C level is a useful alternative to LDL-C level.
- LDL-C thresholds and targets are likely to be supplemented and eventually replaced by their non-HDL-C equivalents.
- The levels of non-HDL-C are usually approximately 0.5 to 0.8 mmol/L higher than corresponding LDL-C levels.
- Lipid and lipoprotein levels need to be considered in the context of other risk factors.
- The NVDPA Australian risk calculator should be used to estimate the absolute risk of cardiovascular disease in the following five years for patients who do not fit into any of the very high clinical risk categories.
- Interpretation of total cholesterol level, which is a combination of pro- and antiatherosclerotic components, is confounded. It is more appropriate to be guided by the LDL level or, preferably, the non-HDL-C level.

to cholesterol depletion of LDL and HDL. Thus hypertriglyceridaemia is often associated with a low HDL-C level and the presence of so-called 'small, dense' LDL. The latter is significant because the LDL-C level may not reflect the greater number and atherogenicity of the particles present.[8] There are several measurements, including apolipoprotein B (apoB) level and LDL particle number (LDL-P), that compensate for this problem but calculation of the non-HDL-C level is likely to be sufficient for most situations. In future, it is possible that use of LDL-C levels as treatment targets or thresholds for clinical decisions may be augmented or superseded by use of non-HDL-C levels. This process may be accelerated by the introduction of new drugs that render LDL-C level calculated by the Friedewald equation inaccurate. The non-HDL-C threshold and target levels are likely to be approximately 0.5 to 0.8 mmol/L higher than their LDL-C counterparts.

Mr PT's non-HDL-C level is 5.8 mmol/L. This is undesirably high but clinical decisions should be based on his calculated absolute risk of CVD. The presence of diabetes favours continuation or introduction of statin therapy, and the persistence of a high triglyceride level and a low HDL-C level could warrant addition of fenofibrate. The treatment targets should be total cholesterol less than 4.0 mmol/L, HDL-C 1 mmol/L or higher, LDL-C less than 2.0 mmol/L, non-HDL-C less than 2.5 mmol/L and triglycerides less than 2.0 mmol/L.[1]

Case 2. **Ms AH is a 34-year-old woman with type 1 diabetes who has returned for review. Her lipid profile reveals: total cholesterol, 8.1 mmol/L; triglycerides, 1.1 mmol/L; and HDL-C, 2.8 mmol/L. The laboratory has calculated the LDL-C to be 4.7 mmol/L. She is asymptomatic and has never suffered CVD or other serious illness. Her other results are free from any suggestion of alterations in renal, hepatic or thyroid functions. She is slightly overweight (BMI, 27 kg/m^2), normotensive and a lifelong nonsmoker. These results are relatively unchanged from a previous test three months ago.**

Does her hypercholesterolaemia warrant further evaluation or intervention?

It is recommended that absolute risk of a cardiovascular event within the next five years, according to NVDPA (or equivalent) guidelines, should be calculated to assist management of cases of primary prevention (i.e. in those instances in which a clinical atherothrombotic coronary or cerebrovascular event has not yet occurred).[1,2] Superficially, the clinical information and laboratory results are sufficient to permit the calculation of this patient's absolute risk of CVD. On the other hand, it is recognised that some clinical situations, such as longstanding diabetes or chronic renal impairment, constitute sufficiently high risk to warrant an aggressive approach to risk factor intervention irrespective of calculated risk. Likewise, very high levels of atherogenic lipoproteins or blood pressure are categorised as very high risk because the epidemiological studies on which absolute risk calculations are based contain very few individuals with such severe risk factor profiles, and hence there is uncertainty concerning the calculation. Consequently the fact that this patient's total cholesterol level exceeds 7.5 mmol/L could be taken as evidence of very high risk necessitating an aggressive approach to risk factor control.

However, this approach is not above criticism because total cholesterol is a confounded measurement that combines pro- and antiatherosclerotic lipoprotein fractions. Clinicians would recognise that the picture of elevated total cholesterol with well-sustained HDL-C is common, particularly among women. Insulin therapy in people with type 1 diabetes may further increase HDL-C. In cases such as Ms AH, the calculation of the non-HDL-C level (or LDL-C level) yields a result that is less alarming. Furthermore, the use of the relevant total cholesterol and HDL-C levels in an absolute risk calculator results in a proportionately lower level of CVD risk that in many instances is consistent with clinical experience. Clearly this patient has more than adequate levels of HDL-C. The question is the degree to which the proatherosclerotic fractions (reflected by LDL-C level or the more simply calculated non-HDL-C level) are increased.

Ms AH's LDL-C level is 4.8 mmol/L and her non-HDL-C level is 5.3 mmol/L. Severely elevated levels would represent more of a risk for future CVD, even in the presence of elevated HDL-C.[5] As they stand, the LDL-C level is below 5.0 mmoL/L and non-HDL-C level is below 5.5 mmoL/L. If this patient did not have diabetes, it could be argued that dietary control could be intensified by the addition of plant sterol foods. This would be expected to reduce total cholesterol, LDL-C and non-HDL-C by up to 10%. However, the question of whether to add statin therapy also requires consideration of the presence of prolonged diabetes (albeit type 1 in a young adult). As in case 1, the treatment targets should be total cholesterol less than 4.0 mmol/L, HDL-C 1 mmol/L or higher, LDL-C less than 2.0 mmol/L, non-HDL-C less than 2.5 mmol/L and triglycerides less than 2.0 mmol/L.[1]

Conclusion

Nonfasting lipid results can contribute to assessment of CVD risk in that nonfasting total cholesterol and HDL-C levels can provide

the necessary lipid and lipoprotein components for the estimation of absolute risk using an absolute CVD risk calculator while the difference between total cholesterol and HDL-C, which is referred to as non-HDL-C, is a more than adequate alternative for LDL-C. A fasting triglyceride level is only required to formally diagnose hypertriglyceridaemia or if LDL-C is to be calculated In the usual fashion, using the Friedewald equation. Practice points are summarised in the Box.

Clinical situations such as long-standing diabetes or chronic renal impairment are among the factors that are considered to constitute sufficiently high risk to warrant an aggressive approach to risk factor intervention irrespective of calculated risk. A total cholesterol level above 7.5 mmol/L is also considered to be in this category. Total cholesterol, however, represents a combination of pro- and antiatherosclerotic components and its interpretation may be confounded, particularly when total cholesterol is elevated in the presence of an elevated HDL-C level (as in the discussed case of a young adult woman with type 1 diabetes). In such situations, it is more appropriate to be guided by the LDL level or, preferably, the non-HDL-C level, taking into consideration the presence of diabetes. **ET**

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