Re-assessing the role of non-fasting lipids; a change in perspective

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Introduction

Lipid testing plays a major role in cardiovascular risk stratification and management in clinical practice. Despite the fact that we spend the vast majority of our time in a non-fasting state, fasting samples have long been the standard for measurement of triglycerides and cholesterol, as fasting is believed to reduce variability and allow for a more accurate derivation of the commonly used Friedewald-calculated low-density lipoprotein (LDL) cholesterol. Another reason for preferring fasting lipid profiles has been the concern for an increase in triglyceride concentration seen after consuming a fatty meal (i.e., a fat tolerance test). However, the increase in plasma triglycerides observed after habitual food intake is much less than that observed during a fat tolerance test, making this concern less of a concern. In addition, recent studies suggest that postprandial effects do not weaken, and may even strengthen, the risk associations of lipids with cardiovascular disease (CVD). If postprandial effects do not substantially alter lipid levels or their association with cardiovascular risk, then a non-fasting blood draw has many practical and possibly economic advantages (1).

Specific attention should also be directed to the fact that in certain patients, such as diabetics, fasting may mask abnormalities in triglyceride-rich lipid metabolism, which may be pivotal in identifying those with continued residual risk despite statin treatment. Recently the joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine suggest that non-fasting lipids become the new standard for lipid measurement, with fasting levels obtained only in specific situations (*Table 1*).

Effects of the postprandial state on lipid levels and risk assessment

The major concern of clinicians regarding non-fasting lipid measurements is the variable effect of the postprandial state on lipid levels. There are, however, several studies to date that have shown that most lipid levels differ minimally after a meal compared with fasting. Clinically insignificant changes are seen; negligible changes for high-density lipoprotein (HDL) cholesterol; slight changes (up to 8 mg/dL) for total cholesterol, LDL cholesterol, and non-HDL cholesterol; and modest changes (up to 25 mg/dL) for triglycerides (2). In addition, CVD risk from numerous large prospective studies, over the past several decades have consistently found that non-fasting lipids are sufficient for general screening of cardiovascular risk (8-10). Both clinical events (e.g., myocardial infarction, stroke, and coronary revascularization) and mortality have been assessed in these studies, finding consistent associations for non-fasting lipids with CVD. Those studies that have included both fasting and non-fasting groups of patients have shown either similar, at times even greater, CVD risk associations for non-fasting lipids (including for LDL cholesterol and triglycerides) compared with fasting lipids.

In addition, a meta-analysis from 68 prospective studies, 20 of which used non-fasting blood samples, found no attenuation of lipid relationships with predicting incident

Table 1 Summary of key guideline and consensus recommendations on fasting for lipid testing

Guideline or statement	Year	CVD risk assessment or before starting lipid lowering therapy	During lipid lowering therapy	Non-fasting triglycerides
European Atherosclerosis Society/European Federation for Laboratory Medicine (2)	2016	Fasting lipids are not routinely required	Fasting is not required if patients are on stable drug therapy	For triglycerides >~400 mg/dL (5 mmol/L), fasting may be considered; refer to a specialist Non-fasting triglycerides ≥175 mg/dL (2 mmol/L) is elevated
National Clinical Guideline Center (NICE) and Joint British Societies Guidelines (3)	2014	A fasting sample is not needed	Consider an annual non-fasting non-HDL cholesterol	For triglycerides >20 mmol/L (880 mg/dL), refer to a specialist For triglycerides between 10 and 20 mmol/L (880 to 1,770 mg/dL), repeat fasting
American College of Cardiology/American Heart Association Guidelines (4)	2013	A fasting sample is preferred (but not mandatory)	Fasting lipids to assess per cent reduction in LDL cholesterol and adequate response to statin therapy	Elevated non-fasting triglycerides ≥200 mg/dL should be repeated fasting If ≥500 mg/dL, screen for secondary causes
Canadian Cardiovascular Society Guidelines (5)	2012	Non-HDL cholesterol has the advantage of being applicable in a non-fasting state	LDL cholesterol is the primary target of therapy Non-HDL cholesterol (fasting or non-fasting) as an alternate primary target	
European Society of Cardiology/European Atherosclerosis Society (6)	2011	If possible (for triglyceride and LDL cholesterol), blood sampling should be made after fasting 12 hours	(Fasting) LDL cholesterol is treatment target	
		Total and HDL cholesterol can be determined in non-fasting samples	(Fasting or non-fasting) Non-HDL cholesterol is secondary target in people with diabetes, metabolic syndrome, combined hyperlipidemias, or chronic kidney disease	
Canadian Hypertension Education Program Guidelines (7)	2016	A fasting sample is no longer required, non-fasting is equally appropriate.	Not applicable	Not applicable

events (N=103,354; number of events 3,829) for non-fasting lipids (10). Finally, at least three large statin clinical trials have used non-fasting lipids (involving nearly 43,000 patients) (10). The overall evidence from these findings suggests that measuring non-fasting lipids confers no disadvantage with respect to risk assessment, and in certain instances may be preferred.

Safety and economic benefits

While there are no studies to date specifically assessing the cost-effectiveness of fasting versus non-fasting lipid testing, it is not difficult to surmise that non-fasting lipids would be more economical and safer for certain groups of patients, such as diabetics. In fact, according to a pilot study by Aldasouqi *et al.* (11) up to 27.1% of diabetic patients experience a fasting-evoked en-route hypoglycemic event due to fasting for blood tests. These events are vastly under reported and add considerably to patient morbidity, suggesting that a shift in practice is mandated for these patients.

It is also important to note, as is mentioned in the EAS and EFMS joint committee recommendations, that obtaining a non-fasting screening test in no way precludes the use of a second fasting test if clinically indicated. In the Danish experience (where a non-fasting lipid profile has been the standard since 2009) (2), only 10% of patients who underwent non-fasting lipid profiles needed repeat laboratory testing for a fasting panel.

As is well known, improvements in quality and efficiency result in decreased healthcare expenditures. In terms of fasting lipids, many patients are not fasting on initial evaluation by their providers resulting in a repeat visit if a lipid profile is indicated. Patients are often required to expend additional resources to return to a laboratory for fasting levels and some may forgo coming back altogether. If patients return for their doctors' appointment without testing, this resultant follow up visit is one where key laboratory data is not available and often management decisions are deferred. These visits consume additional health care dollars and resources, and also potentially deprive other patients from access to needed care, as well as adding to length of patient waiting times.

Coupled to patient inconvenience, healthcare practitioners who send patients for fasting blood work on an alternate day, bear the responsibility of ensuring these tests occur, which adds additional burden on already overwhelmed practitioners and generates system wide inefficiencies. From a laboratory perspective, requiring routine fasting lipid samples may also reduce laboratory workflow efficiency due to the early morning congestion of visits for lipid testing. All of these factors would contribute to lack of efficiency and quality in the health care system and consequently to increased health care costs.

Guidelines and recommendations

It is with all of these findings in mind, that recommendations for the clinical use of non-fasting lipids have become more widespread. The evolution of recommendations of different expert panels and societies is summarized in *Table 1* and highlights the growing evidence base for non-fasting lipid testing. It is not a new finding that practice guidelines allow for the measurement of non-fasting total and HDL cholesterol (and hence the calculated values from these: non-HDL cholesterol and the total/HDL cholesterol ratio) (12), since levels of these lipids are essentially unaltered when measured in fasting or non-fasting specimens. In the U.S., the third report of the Adult Treatment Panel (ATP III, 2001) (12) the 2013 ACC/AHA cholesterol guidelines (4) both recommended that initial screening should include a fasting lipid profile, although they allowed for measuring non-fasting total, HDL, and non-HDL cholesterol (12).

However over the past few years, a shift in practice recommendations has occurred. The National Clinical Guideline Center (NICE) and Joint British Societies recommended in 2014, that a fasting sample is not needed for routine clinical care (3). Most recently, in 2016, the European Atherosclerosis Society and the European Federation of Laboratory Medicine recommended using non-fasting lipid testing for routine clinical practice and provided specific cut-points for desirable fasting and non-fasting lipid levels (2). Elevated non-fasting triglycerides were defined as ≥175 mg/dL (≥2 mmol/L) (2,13), and repeat measurement of fasting triglycerides were suggested when non-fasting levels are greater than ~400 mg/dL (2). In a change from their previous recommendations, the 2016 Canadian Hypertension Education Program guidelines have now removed fasting as a requirement from lipid testing. This major shift in newer guidelines reflects the changing focus of risk assessment from LDL to non-HDL cholesterol (apolipoprotein B) as a better predictor of risk.

Limitations of evidence

Currently there are no studies assessing the predictive value of lipids measured both fasting and non-fasting from

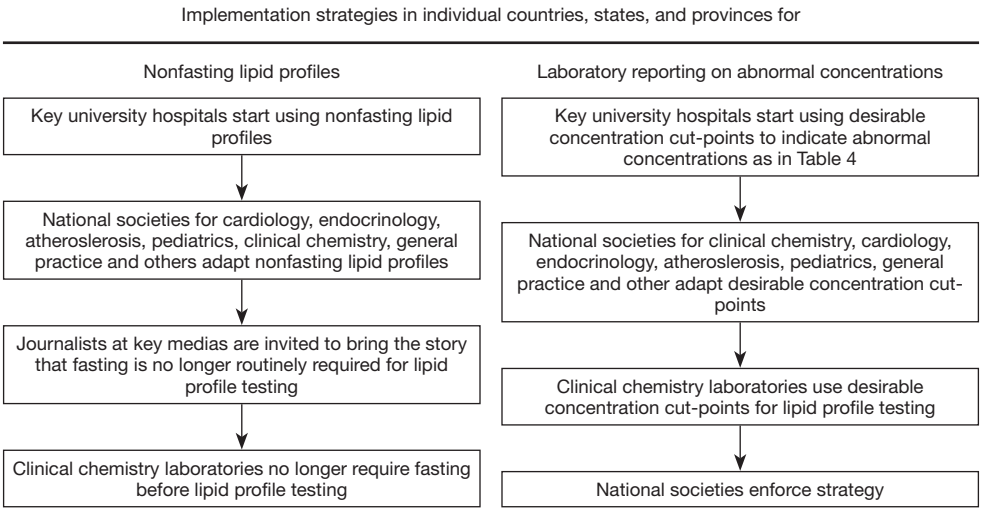

Figure 1 From the EAS and EFMS Joint Commission Statement, EHJ March 15, 2016. [Nordestgaard BG, Langsted A, Mora S, *et al.* Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points—a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. European Heart Journal Jul 2016;37:1944-58. Reprinted by permission of Oxford University Press on behalf of the European Society of Cardiology.This image/content is not covered by the terms of the Open Access licence of this publication. For permission to reuse, please contact the rights holder.]

the same individuals, and no randomized outcomes trials or cost-effectiveness analyses. More data is also needed assessing individuals from different ethnic backgrounds.

Conclusions

In summary, robust evidence supports the use of non-fasting blood draws for routine clinical practice and widespread adoption would be favorable for both patients and healthcare providers. The fasting panel now has a much more limited role, predominantly in the setting of abnormally high triglycerides and prior to starting treatment in patients with genetic lipid disorders. For the majority of patients though, the non-fasting test is safe, convenient and reflects an improvement in health care delivery. Methods to bring this testing strategy into mainstream clinical practice have been suggested by the EAS and EFLM consensus statement shown in *Figure 1* (1). The sooner this occurs, the sooner the benefits of efficient health care will be realized for patients and practitioners alike.

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Footnote

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Comment on: Nordestgaard BG, Langsted A, Mora S, *et al.* Fasting Is Not Routinely Required for Determination of a Lipid Profile: Clinical and Laboratory Implications Including Flagging at Desirable Concentration Cutpoints-A Joint Consensus Statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem 2016;62:930-46.

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