NOT SO FAST:
A Critical Look at the Trend Toward Non-Fasting Lipid Panels
Most patients are familiar with the lipid testing routine. Up bright and early, and out the door without so much as a cup of juice. On arrival at the lab, they are greeted by a crowd of fellow patients. Most will not see their doctors until that afternoon or possibly later in the week. In other situations, a doctor requests a lipid panel following a clinical evaluation, in which case the patient makes a separate return trip after an overnight fast.

Patients certainly shoulder most of the burden surrounding fasting blood draws, but clinical labs are a close second. Clinical laboratorians take pride in minimizing patient wait times and providing the highest quality testing.

Outpatient laboratories in particular design workflows, staffing models, and equipment to accommodate the early morning rush of patients needing their blood drawn so they can go eat breakfast. At my own institution, 80% of all outpatient lipid testing occurs between 6:30 and 10 a.m. Scheduling blood draws throughout the day would be much more cost-effective. However, lipids are measured on fasting samples. Everyone knows that. That’s the way things have always been. Now, however, the rules might be about to change.

After decades of dogma requiring an overnight fast prior to blood collection for lipid measurements, several prominent medical societies have recently endorsed the routine use of non-fasting lipids (Table 1) (1-6). This shift toward nonfasting has stimulated much debate. Laboratorians certainly do not want to sacrifice quality for the sake of convenience. However, new studies directly assessing the impact of fasting on lipid measures have provided sufficient data to support the claim that non-fasting lipid testing is evidence-based medicine that provides superior care for the majority of patients.

Why Do We Measure Fasting Lipids?
Lipids, specifically low-density lipoprotein cholesterol (LDL-C), are measured to assess an individual’s risk of coronary artery disease and
monitor a patient’s response to lipid-lowering therapy. The association between LDL-C and heart disease is arguably one of the most studied in medicine. Dozens of prospective clinical trials have established that the risk of heart disease is directly proportional to blood levels of LDL-C. Furthermore, interventional trials have shown that lowering LDL-C reduces risk of heart disease. This remains true regardless of baseline LDL-C and has no apparent limit in efficacy—the lower the better.

LDL-C is not a specific molecule, but rather a measure of all blood cholesterol contained in lipoproteins with a density between 1.019 and 1.063 g/L. Separating blood via density gradient is time-consuming, laborious, and expensive. The most common laboratory method estimates LDL-C according to the Friedewald formula: LDL-C = [Total Cholesterol] – [HDL-C] – [Triglycerides/5]. Although it was derived from a small number of subjects and intended for research purposes, the Friedewald formula made possible the rapid and ubiquitous adoption of LDL-C measures as standard clinical care.

In Friedewald’s highly cited original publication, the authors mention that fasting samples are necessary to reduce the variability observed in measured triglycerides (7). Indeed, it is well established that triglyceride concentrations transiently increase following a meal due to the presence of chylomicrons (8). Furthermore, the degree of triglyceride elevation is related to the amount of fat consumed (9) and the patient’s baseline triglyceride concentration (1). “Aha!” exclaims the discerning clinical laboratorian. “Not fasting alters measured results. Case closed. The absurdity of non-fasting lipid panels is put to rest.” But there’s more to the story.

The Clinical Significance of Increased Non-Fasting Triglycerides
On closer inspection, the most recent data suggest that triglyceride changes observed due to non-fasting are clinically negligible in most patients. In one study of >140,000 individuals, 80% of subjects had non-fasting triglyceride concentrations <195 mg/dL (10). Another study of >33,000 subjects found that the median concentration of non-fasting triglycerides was 124 mg/dL, while 75% of patients had values <185 mg/dL (8). These findings are supported by the Very Large Database of Lipids (n=1.4 million patients). This study found a median non-fasting serum triglyceride concentration of 125 mg/dL with 75% of patients having a non-fasting triglyceride value <182 mg/dL (11).

The fact that most patients have relatively normal concentrations of triglycerides (<150 mg/dL) even in the non-fasting state is good news. As noted previously, post-prandial elevation of triglycerides is directly proportional to fasting triglyceride concentrations: The higher a patient’s fasting triglycerides, the larger the increase will be following a meal. This phenomenon was recently affirmed in a study of 5,538 patients with matched lipid panels measured immediately before and 3 to 5 hours after a meal (12). The median post-prandial increase in triglycerides was 50-75% among patients with fasting triglycerides >250 mg/dL. However, patients with fasting triglycerides <130 mg/dL had an average increase of 6 mg/dL or less following a meal (<5%). In larger studies, the median peak post-prandial triglyceride increase was 26 mg/dL, or 21% from the median baseline of 124 mg/dL (8).

The biological variability of fasting triglycerides is reported to be 20-30%, and the intra-individual variability ranges from 5% for people with average fasting triglycerides <100 mg/dL to 75% for those with average fasting triglycerides >250 mg/dL (13). Consequently, a triglycerides increase of 6 mg/dL, 26 mg/dL, or even 36 mg/dL based on a non-fasting sample is well within the noise of typical biological variations.

There is an apparent disconnect between these studies and the historical understanding of fasting influence on triglycerides. A possible explanation is that many historical studies measured triglycerides following an intentionally high fat meal (50 g or more). A typical meal containing approximately 17g of fat maximally increases triglycerides by <20% (9). Obviously, if a patient reports for a blood draw after an all-American lunch of a cheeseburger,
NEARLY 20% OF PROM PATIENTS EXHIBIT VAGINAL BLEEDING

Actim® PROM
The Only PROM Test Proven Effective in the Presence of Whole Blood and Other Common Contaminants

Why risk inaccurate diagnosis when there’s one PROM test proven effective for patients with vaginal bleeding. For more than 20 years, Actim PROM has been used to effectively diagnose more than 5 million PROM patients worldwide. Now available in the U.S. at a special introductory price. Contact us at 800.243.2974 or www.coopersurgical.com.

Endorsement of Routine Non-Fasting Lipid Panels

<table>
<thead>
<tr>
<th>Year</th>
<th>Society</th>
<th>Non-Fasting Triglycerides cutoff*</th>
<th>Risk Assessment (Prior to Therapy)</th>
<th>Lipid Assessment on Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>European Atherosclerosis Society and European Federation for Laboratory Medicine</td>
<td>&gt;400 mg/dL</td>
<td>Non-fasting lipid panel is appropriate.</td>
<td>Non-fasting lipid panel is acceptable.</td>
</tr>
<tr>
<td>2014</td>
<td>National Clinical Guideline Center and Joint British Societies</td>
<td>&gt;400 mg/dL</td>
<td>Non-fasting lipid panel is acceptable.</td>
<td>Non-fasting lipid panel is acceptable.</td>
</tr>
<tr>
<td>2013</td>
<td>American College of Cardiology / American Heart Association</td>
<td>&gt;200 mg/dL</td>
<td>Fasting lipid panel is preferred but not required.</td>
<td>Fasting lipid panel recommended prior to statin initiation. Non-fasting is acceptable on treatment follow-up.</td>
</tr>
</tbody>
</table>

*Repeat measure of triglycerides using fasting sample is recommended following elevated non-fasting triglycerides.

of 586,481 patients with median triglyceride concentrations of 125 mg/dL (interquartile range [IQR] 87-182), the median ultracentrifugemeasured LDL-C was 115 mg/dL (IQR 91-142), while the median Friedewald estimated LDL-C was 112 mg/dL (IQR 87-139) (11). Another study comparing fasting and non-fasting LDL-C (estimated by the Friedewald formula in both cases) among 209,180 community outpatients showed an average decrease of 4 mg/dL LDL-C due to non-fasting (22).

Two factors help minimize the impact of fasting on estimated LDL-C. First, as explained above, the typical increase in triglycerides is less than previously assumed. Second, estimated LDL-C is only reduced by 1 mg/dL for every 5 mg/dL increase in triglycerides. Since most patients have at most a non-fasting increase of 25 mg/dL triglycerides, then LDL-C estimates are only expected to vary by 5 mg/dL.

The Clinical Significance of Decreased Non-Fasting LDL-C

Clinicians use LDL-C to establish a patient’s risk of cardiovascular disease and to monitor the impact of therapeutic interventions. The primary tools used to assess a patient’s risk of cardiovascular disease are the Framingham Score, the American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equation, the Reynolds score, and European Systematic Coronary Risk Evaluation Score. All of these calculations incorporate age, sex, blood pressure, smoking status, total cholesterol, and HDL-C. None formally include triglycerides or LDL-C; the endorsed means of risk assessment are completely independent of a patient’s fasting status.

Data from 8,270 patients enrolled in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) confirm the rationale for excluding these measures. In ASCOT, investigators found greater than 95% concordance between fasting and non-fasting lipids using the 2013 ACC/AHA Pooled Cohorts equation (23). Incidentally, this study found that non-fasting LDL-C was a stronger indicator of
future cardiac events within 3 years when compared to fasting LDL-C.

Previous strategies supported lower target LDL-C for higher risk patients. In order to achieve lower target LDL-C, clinicians treated high-risk patients more aggressively and these individuals received much more benefit. Patients who had borderline high lipids were prescribed a weaker dosage of lipid-lowering drugs or none at all.

These days lipid management strategies no longer endorse a target LDL-C or prescribed dosage of lipid-lowering medications. Rather, the new ACC/AHA recommendations call for prescribing a specific dosage of statins based on a patient’s baseline risk (24). This recommendation is based on data from dozens of randomized clinical trials and is in agreement with the concept of “the lower the better.” ACC/AHA do not recommend a fasting lipid panel prior to starting statin therapy or adjusting dosages. However, initial screening and long-term monitoring of lipid lowering are minimally affected by non-fasting.

As a thought experiment, consider two lipid scenarios for a hypothetical patient (Table 2). In the first scenario, a fasting sample has a calculated LDL-C of 162 mg/dL (high by conventional terminology). As triglycerides increase due to non-fasting, the calculated LDL-C is reduced. Assuming this is an initial screen, then calculated risk is the criterion of interest, and fasting has no impact. If this were an annual follow-up for a patient on therapy, even a triglyceride increase of 50% would result in a reported LDL-C of 143 mg/dL (borderline high). This difference is of questionable clinical import. Furthermore, a non-fasting triglyceride >200 mg/dL would trigger a request for a follow-up fasting lipid panel.

In the second scenario, the fasting sample has a calculated LDL-C of 194 mg/dL, suggesting familial hypercholesterolemia. Calculated LDL-C falls to 188 mg/dL if triglycerides increase 20% (the median increase) for a non-fasting sample. In this worst case scenario, the calculated LDL-C falls below the diagnostic threshold due to the non-fasting elevation. However, the reported LDL-C in non-fasting...
state is within 2.7% of the fasting value. This variation is within the biological noise and even within the analytical noise of measured cholesterol. Thus, a similar change in values could be seen in serial fasting measures.

**Non-Fasting LDL-C and Risk of Heart Disease**

While it is true that most studies to date have used fasting measures of LDL-C to establish cardiovascular risk, several prospective studies have reported on the utility of non-fasting LDL-C (1, 15, 25, 26). The Emerging Risk Factors Collaboration reported a meta-analysis of 68 prospective studies and found no difference in the association of lipids with risk of heart disease within the 20 studies that used non-fasting lipids (25). Among these 20 studies, three were randomized clinical trials demonstrating the efficacy of statin interventions in nearly 43,000 patients.

**Laboratory Implementation of Non-Fasting Lipid Panels**

From the laboratory perspective, it would be prudent to report non-fasting triglycerides and LDL-C differently from fasting samples. This would enable laboratories to use a unique abnormal flag for non-fasting triglycerides at the recommended 200 mg/dL cutpoint and automatically appended a comment suggesting repeat testing after an 8-12 hour fast. Due to the novelty of reporting non-fasting Friedewald estimated LDL-C, including an appended comment that suggests values may be decreased when triglycerides are >200 mg/dL would also be reasonable.

In conclusion, multiple independent and highly powered studies suggest that non-fasting lipids are similar (or better) than fasting measures for predicting risk of cardiovascular disease. Furthermore, routine non-fasting lipid panels can accommodate a majority of patients without the need for separate fasting visits. Thus, routine non-fasting lipids are not only convenient, but also evidence-based. These findings empower laboratories to build a new paradigm for lipid testing that better accommodates most patients while maintaining high-quality care for special cases of dyslipidemia.

**Jeffrey Meeusen, PhD**

is co-director of cardiovascular laboratory medicine and a senior associate consultant in the division of clinical core laboratory services at Mayo Clinic in Rochester, Minnesota.

**REFERENCES**


