Editorial Commentary

Non-HDL-C/TC ratio: a useful screenings test for dysbetalipoproteinemia

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Familial dysbetalipoproteinemia (FD) is a genetic lipid disorder, caused by a mutation in the apolipoprotein E (*APOE*) gene, and characterized by an increased number of cholesterol-enriched remnant lipoproteins in the plasma and premature cardiovascular disease. In the Frederickson classification of lipid disorders, FD was initially described as type III hyperlipoproteinemia (1). Usually FD patients respond well to dietary restrictions (2) and treatment with statins and fibrate in combination (3). Early diagnosis of FD is important for timely treatment, including risk factor management, dietary advice and drug treatment, as well as screening of family members. Unfortunately FD is often overlooked in the differential diagnosis of combined hypertriglyceridemia and hypercholesterolemia (4), mainly due to the fact that clinical clues are often lacking and the formal diagnosis needs specialized laboratory testing.

The diagnosis FD was originally defined as a VLDL-cholesterol (VLDL-C)/plasma triglyceride (TG) ratio of >0.30 (or >0.69 in mmol) as determined by ultracentrifugation; and/or as the presence of a broad-beta band in the VLDL range on agarose gel electrophoresis (β-VLDL) (5). In 90% of the cases FD is associated with the homozygous ε2ε2 genotype of the *APOE* gene, which can cause impaired remnant clearance in the presence of insulin resistance (6,7). However, 10% of FD is caused by other (rare, often dominant) mutations in the *APOE* gene (7). Because ultracentrifugation and electrophoresis are laborious and costly and therefore nowadays not used in routine clinical care, there is a clinical need for an easy to use screenings test to select patients for further diagnostic work up including *APOE* genotyping.

Boot and colleagues from the United Kingdom provide evidence for the use of the non-HDL cholesterol to apolipoprotein B (non-HDL-C/apoB) ratio to clinically screen for FD (8). The authors retrospectively included all patients (N=1,637) referred to their clinic for diagnosis of FD. In 63 patients FD was established, defined as a VLDL-C/plasma TG ratio >0.69 and the presence of β-VLDL using a method that combines ultracentrifugation and polyanionic precipitation. In FD patients, the mean non-HDL-C/apoB ratio was 7.3±1.5 mmol/g compared to 4.0±0.5 mmol/g in non-FD patients. When using an optimal cutoff of non-HDL-C/apoB, >4.91 mmol/g, the sensitivity for FD was 95% (95% CI, 94–96) and specificity 95% (95% CI, 93–96). Furthermore, the positive predictive value (PPV) was 43.6% (95% CI, 35.2–52.2) and negative predictive value (NPV) 99.9% (95% CI, 99.5–100).

The authors compare their new method with several previously described alternatives, i.e., the TC/apoB ratio and two apoB based algorithms. In the original article by Blom *et al.* an apoB/TC ratio <0.15 had a sensitivity of 89% (95% CI, 78–96%) and a specificity of 97% (95% CI, 94–98%), when using a VLDL-C/VLDL-TG ratio ≥0.96 or a VLDL-C/plasma TG ratio ≥0.69 and an ε2ε2 genotype as the gold standard (9). It is not completely clear why the Boot *et al.* used TC/apoB instead of apoB/TC as published by Blom *et al.* (9), possibly for comparative purposes. Boot *et al.* find the optimal cutoff for TC/apoB to be >6.55 mmol/g with a sensitivity and specificity of 92% (95% CI, 82–97%) and 95% (95% CI, 93–96%), and PPV and NPV of 40.0% (95% CI, 32.0–48.5) and 99.7% (95% CI, 99.2–99.9)

respectively. The non-HDL-C/apoB ratio was not influenced by sex, while the TC/apoB ratio was.

The first apoB based algorithm by Sniderman *et al.* found an AUC-ROC of 98.8% (95% CI, not given) for diagnosis of FD when TC/apoB ratio ≥6.2 and TG/apoB ratio <10 (10). Their gold standard was a TG >75th percentile for age and gender, VLDL-C/plasma TG >0.69 and presence of an ε2ε2 genotype. The second apoB algorithm, designed by the same group, uses apoB <1.2 g/L, TG ≥1.5 mmol/L, TG/apoB <10 and TC/apoB ≥6.2 as diagnostic criterium of FD (11). In the article by Boot and colleagues the diagnostic performance of both TC/apoB and non-HDL-C/apoB was better than that of either apoB algorithm.

Although the non-HDL-C/apoB ratio had a high sensitivity and specificity, the PPV was low (43.6%), meaning that a positive test does not prove the diagnosis of FD. However, the NPV was high, so in the case of a negative test FD is highly unlikely. This makes it a useful screenings test to determine in which patients further diagnostic workup for FD is warranted, including *APOE* genotyping. Based on the comparisons of diagnostic performance made by the authors, the non-HDL-C/apoB ratio seems a slightly better alternative compared to the TC/apoB ratio, possibly due to confounding effects of HDL-C.

In conclusion, a screenings test for FD that can easily be used in clinical practice could aid clinicians to select patients with mixed hyperlipemia (i.e., high total cholesterol and high triglycerides) for further diagnostic workup for the diagnosis of FD, including *APOE* genotyping. A non-HDL-C/apoB ratio <4.91 mmol/g, as elegantly shown by Boot and colleagues in the February issue of *Clinical Chemistry* of this year, is a useful test to rule out the presence of FD and spare unnecessary further diagnostic testing.

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Footnote

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