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Quantification of concordance and discordance between apolipoprotein-B and the currently recommended non-HDL-cholesterol goals for cardiovascular risk assessment in patients with diabetes and hypertriglyceridemia☆

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ABSTRACT

Aims: In patients with diabetes and hypertriglyceridemia, LDL-cholesterol (LDL-C) provides an inaccurate reflection of LDL particle burden. The relative value of non-HDL-cholesterol (non-HDL-C) and apolipoprotein-B (Apo-B) in estimating cardiovascular risk is controversial. We assessed the discordance between non-HDL-C and Apo-B targets in patients with diabetes with TG 200–499 mg/dl.

Methods: Data from 1430 determinations of LDL-C, non-HDL-C, and Apo-B in ambulatory patients with diabetes were analyzed. Rates of discordance were calculated, based on the currently recommended LDL-C, non-HDL-C, and Apo-B goals.

Results: In patients with non-HDL-C goal of <130 mg/dl, there was a discordance with Apo-B level goal of <90 mg/dl, in 31% of samples. In patients with non-HDL-C goal of <100 mg/dl, 6% of samples had Apo-B ≥80 and 18% had Apo-B <80 mg/dl. Using the Apo-B goal of <70 mg/dl, these numbers were 37% and 3.5% respectively. There was also a significant gender difference, i.e. under-estimation of risk by suggested non-HDL-C cut-offs, in females, compared to males.

Conclusions: In patients with diabetes and hypertriglyceridemia, a considerable discordance exists between non-HDL-C and Apo-B. Our data suggest a need for prospective studies to compare the relative merits of non-HDL-C and Apo-B targets in the assessment of cardiovascular risk.

There is epidemiologic evidence that average LDL-cholesterol (LDL-C) levels in the United States adult population are declining [1], while the triglyceride (TG) levels have been rising during the past two decades [2]. According to the Adult Treatment Panel III (ATPIII) panel of the National Cholesterol Education Program, normal serum TG concentration is defined as a level <150 mg/dl in the fasting state, whereas a level ≥200 is considered "high" [3]. These cut-offs were recently endorsed by the scientific statement of the American Heart Association [4]. According to the National Health and Nutrition Examination Survey (NHANES, 1999-2002), ~35% of the adults with type 2 diabetes have fasting TG ≥200 mg/dl [5]. With the

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increasing prevalence of obesity, metabolic syndrome, and diabetes, the current prevalence is likely to be even higher, particularly in certain ethnic populations.

It is widely appreciated that in the presence of elevated TG, LDL particle composition is altered such that LDL-C levels may underestimate the LDL particle number (LDL-P), and therefore the atherogenic burden. The achieved LDL-C goals in such patients therefore may not fully reflect the residual cardiovascular risk conferred by the actual LDL particle burden. The direct measurement of LDL-P by NMR technique is neither practical nor widely applicable in the clinical setting. It was therefore recommended by the ATPIII panel, that in the presence of high TG (200–499 mg/dl), non-HDL-cholesterol (non-HDL-C), as an indirect estimate of all Apo-B particles, should be targeted as a secondary goal [3]. However, apolipoprotein-B (Apo-B) concentration should be physiologically a better surrogate for LDL-P, than non-HDL-C. The chemical assays for Apo-B are now standardized and more widely available. A number of population-based studies have shown Apo-B to be superior to non-HDL-C in the risk assessment [6–10]. However, this view is not accepted by all [4,10–13]. The combined consensus statement by the American Diabetes Association (ADA) and American College of Cardiology (ACC) panel in 2008 recommended that, despite current controversy, both Apo-B and non-HDL-C be considered in the risk assessment of all patients with increased cardiometabolic risk, with or without diabetes, and provided risk-specific ''cut-offs'' for Apo-B, and non-HDL-C goals [10]. It was also acknowledged by the panel that the two measurements are highly correlated, but with some discordance in patients with hypertriglyceridemia. Most recently, this issue was further addressed by the Expert Panel of the National Lipid association (NLA), and they recommended a more aggressive Apo-B goal of <70 mg/dl, in contrast to ADA/ACC recommendation of <80 mg/dl, in patients with very high cardiovascular risk [14].

There is limited comparative data between non-HDL-C and Apo-B determinations in patients with diabetes. Also, while it is generally believed that non-HDL-C measurements might underestimate cardiovascular risk, compared to Apo-B, it is not clear as to what extent the non-HDL-C measurements might possibly overestimate the risk in some individuals, given other factors, e.g. genetic polymorphism, that might determine Apo-B levels in individuals. We therefore addressed these questions in our ambulatory data base, and explored the degree of concordance and discordance between the two parameters in patients within a wide range of LDL-C levels, in the presence of hypertriglyceridemia.

1. Methods

The data from electronic medical records on all consecutive patients, with serum TG (200–499 mg/dl, seen at the Joslin Diabetes Center, Boston, MA over the course of 12 months (Jan 2009–2010) were collected. As per guidelines of the Institutional Review Board (IRB), all subjects were de-identified, prior to data collection and analyses.

Routine lipid determinations included total cholesterol (Total-C), TG, and HDL-cholesterol (HDL-C), using the Ortho Diagnostics Vitros 5.1 analyzer system. Direct LDL-C assay was measured by the Vitros 2-step dLDL reagents [15]. Non-HDL-C was calculated as the difference between Total-C and HDL-C. For Apo-B measurements, we employed a standardized, immune-turbidometric assay, with coefficient of variation (cv) of <2.05% [16]

The targets of Apo-B <80 and <90 mg/dl for the corresponding LDL-C goals of <70, and <100 mg/dl, and non-HDL-C goals of <100, and <130 mg/dl, respectively, as proposed by the ADA/ACC panel recommendations [10] were used to determine the discordance between Apo-B, LDL-C, and non-HDL-C.

In addition, we performed similar discordance estimates with Apo-B target of <70 mg/dl in those with LDL-C and non-HDL-C goals of <70 and <100 mg/dl respectively, according to the NLA recommendations [14].

Statistical tests were performed in the Joslin Bioinformatics core using standard t tests, regression analyses, and chi square tests as appropriate [17].

The degree of discordance between LDL-C and non-HDL-C, compared to Apo-B, was quantified by kappa analysis [18].

2. Results

There were 1430 samples from 1187 patients (male/female, 58%/42%, mean age 54.9 ± 0.47 year, mean BMI 34.3 ± 2.6, type of diabetes: 80% type 2, 18% type 1, 2%, other).

The mean (±SEM) serum concentrations of lipid levels were as follows, mg/dl:

Total-C, 176.8 ± 1.08
TG, 319 ± 6.9
HDL-C, 44.3 ± 0.39
LDL-C, 86.0 ± 0.72
Apo-B, 91.9 ± 0.66.
The calculated non-HDL-C was 132.5 ± 1.05 mg/dl.

Table 1 presents the distribution of LDL-C <100 and ≥100 mg/dl, and the corresponding non-HDL-C <130 and ≥130 mg/dl, and the discordance of each with Apo-B goal of <90 mg/dl. 76% of the samples were in the LDL-C <100 category, whereas only 51% had non-HDL-C <130 mg/dl. Of those with LDL-C <100, 37.6% exceeded the Apo-B goal of <90; whereas only 7.5% of those with LDLa ≥100 were within the Apo-B goal of <90. On the other hand, of those with non-HDL-C <130, 17.3% exceeded the Apo-B goal of <90; whereas 13.6% of those with non-HDL-C ≥130 were within the Apo-B goal of <90.

Table 2 presents the distribution of LDL <70 and ≥70, and the corresponding non-HDL-C <100 and ≥100, and the discordance of each with Apo-B goal of <80 mg/dl. 22% of the samples were in <70 category, whereas only 9% had non-HDL-C <100 mg/dl. Of those with LDL-C <70, 29.2% exceeded the Apo-B goal of <80; whereas 11.8% of those with LDL ≥70 were within the Apo-B goal of <80. On the other hand, of those with non-HDL-C <100, only 6.1% exceeded the Apo-B goal of <80; whereas 17.8% of those with non-HDL-C ≥100 were within the Apo-B goal of <80.

Table 3 presents the distribution of LDL <70 and ≥70, and the corresponding non-HDL-C <100 and ≥100, and the discordance of each with Apo-B goal of <70 mg/dl. Of those