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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 < 70mg/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

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Conflict of Interest

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“high” (3). These cutoffs 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 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, 11–13). 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 cardio-metabolic 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.

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-Jan 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 < 130mg/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).

Results

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

The mean ($\pm$ 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 < 90mg/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 LDL 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 < 80mg/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 < 70mg/dl. Of those with LDL-C < 70, 64.1 % exceeded the Apo-B goal of < 70; whereas only 1.3 % of those with LDL 70 were within the Apo-B goal of < 70. On the other hand, of those with non-HDL-C

< 100, 37.4 % exceeded the Apo-B goal of < 70; whereas only 3.5% of those with non-HDL-C > 100 were within the Apo-B goal of < 70.

The kappa analyses revealed a “substantial” agreement ($k = 0.690$) between Apo-B target of < 90 and the corresponding non-HDL target of < 130 mg/dl, as defined by Lewis and Koch (18). However, there was only a “moderate” agreement ($k = 0.43-0.597$) between Apo-B < 80 or 70 mg/dl for the corresponding LDL-C targets (< 100 or < 70 mg/dl), or non-HDL cholesterol targets of < 130 and < 100 mg/dl respectively (Tables 1–3).

These distributions were virtually identical when number of patients, rather than number of samples, was analysed (data not shown).

Figure 1 presents the regression line between apo-B and non-HDL-C for the entire group, separately by gender. There was a good overall correlation between the two parameters in each gender (R square 0.74 for males, 0.68 for females). However, the slope of the regression line was significantly different between genders ($P = 0.0016$, by ANCOVA test for heterogeneity of regression slopes), indicating that for a given level of Apo-B, the non-HDL-C values were lower for females, compared to males.

Discussion

In order to better estimate the CVD risk in patients with elevated triglycerides, the ATP III panel recommended a secondary goal of non-HDL-C in patients with TG 200–499, after achieving the primary goal of LDL-C (3). This goal has been endorsed by all major organizations including AHA, ADA, European Atherosclerosis Society (EAS), and others. However, a number of large prospective studies, and meta-analyses, have provided evidence of a better prediction of CVD events with Apo-B determinations, compared to non-HDL-C (6–10). Both Canadian Diabetes Association (CDA) (19) and American Association for Clinical Chemistry (AACC) (8), as well as the 2008 consensus statement from ADA/ACC (10), recommend an Apo-B goal in high risk subjects, based on the current evidence. In a recent extensive analysis of all available studies to date, Sniderman et al have provided further evidence of the superiority of apo-B over non-HDL-C, in the risk of fatal or non-fatal CVD events (9). According to that analyses of 14, head-to-head comparisons, the relative risk ratios for major cardiovascular event estimates by Apo-B, non-HDL-C, and LDL-C were 1.43, 1.34, and 1.25, respectively, with each significantly different from the other.

However, there continues to be some controversy about the relative merits of adding apo-B for risk estimation, particularly from the data by the Emerging Risk Factor Collaboration (11) and others (12, 13, 20). Moreover, the most recent AHA statement on triglycerides and cardiovascular disease (4) does not provide specific goals for Apo-B, while supporting its independent value in risk determination. In a multi-ethnic, multi-national study, INTERHEART, non-HDL-C had a weaker predictive power for myocardial infarction compared to Apo-B (21).

We sought to compare the relationship of LDL-C and non-HDL-C with apo-B in a cohort of patients with diabetes and combined dyslipidemia with TG 200–499, with defined LDL-C and non-HDL-C goals, as reaffirmed by the ATPIII update (22), as well as ADA/ACC (10). Our observation that 29–38 % of values within the LDL-C goal had Apo-B levels above the recommended goal, was not surprising, as it likely reflects the depleted cholesterol content of LDL particles in hypertriglyceridemia (7–10, 23). However, we found considerable discordance between non-HDL-C and Apo-B, while both are recognized to be better predictors of risk, compared to LDL-C. Of particular note was our observation that in 14–18% of observations, apo-B goals of < 90 and < 80 mg/dl were met, but the corresponding

non-HDL-C were 130 and 100 mg/dl respectively. However, using the Apo-B < 70 mg/dl cut-off for very high risk patients as proposed by NLA expert panel (14), there was an excellent concordance with non-HDL-C, with only 3.5% in non-HDL-C 100 category (Table 3). On the other hand, the discordance with non-HDL goal of < 100 mg/dl now reached 37%, and it exceeded 64% for LDL-C goal of < 70 mg/dl. The kappa analysis also revealed that the agreement between Apo-B target of <90 mg/dl and non-HDL-C target of <130mg/dl for moderate to high risk was “substantial, but only “moderate” for Apo-B targets of < 80 or <70 and non-HDL-C of < 100 mg/dl, i.e. those considered to be at very high risk.

Our results support the recommendation that both Apo-B and non-HDL-C should be included in risk assessment, rather than selecting one over the other, since each of these reflects different measures of risk in many individuals due to appreciable differences in lipoprotein particle composition (8–10, 24). Furthermore, substituting Apo-B for non-HDL-C or vice versa may lead to under-treatment in an appreciable number of patients, based on the current cut-offs. It has been reported that the current cut-offs of ApoB at < 80 and < 90 are in fact at a higher percentile distribution in population than the respective LDL-C and non-HDL-C distributions (8, 14). The lack of equivalence between current goals of non-HDL-C and the proposed Apo-B goals is also supported by the data of Ballantyne et al in a large, comparative study of statin-treated patients (25). This issue is particularly relevant to patients with metabolic syndrome, where an increased number of LDL particles is a frequent phenomenon, even after seemingly adequate treatment with statins (26). However, definitive data from clinical trials directly comparing the relative value of non-HDL-C and Apo-B are not yet available.

We studied a diabetes cohort selected on the basis of most common range of high triglyceride, as classified by ATPIII. Our observations are largely in agreement with another large cohort of 2103 males in the Quebec Cardiovascular Study (6). However only 5 % of that cohort had diabetes and the mean LDL-C much higher at 142 mg/dl and TG lower at 155 mg/dl, compared to our cohort. The correlation between non-HDL-C and Apo-B was almost identical in that study, compared to males in our study (R square 0.76 and 0.74 respectively), while the total discordance between non-HDL-C and Apo-B was nearly 30 % in both studies. In the female group in our study, the correlation between the two parameters was weaker at R-square of 0.68, and the slope of the regression line significantly different, compared to males (Fig1). This would support the view that the intensity of treatment based on non-HDL-C alone is even more likely to lead to under-treatment in women, compared to that based on apo-B goals (27). A similar gender difference was noted in the Insulin Resistance and Atherosclerosis Study (IRAS) (28). In that study, the triglyceride levels were significantly higher in diabetic men and women, compared to the respective non-diabetic groups; yet the major differences were seen in diabetic women, with significantly greater apo-B levels in diabetic, compared to non-diabetic women, whereas there was no difference between diabetic and non-diabetic men (28). Using a cut-off point of > 120 mg/dl, 42% diabetic women and 23% of non-diabetic women had high Apo-B ($P < 0.0001$), whereas the corresponding numbers in men were 30% and 26%, respectively ($P = 0.22$).

Although there are limited number of prospective CVD outcome studies to assess the relative merits of Apo-B and non-HDL-C (8–10), the discordance rates we and others have observed raise the need for additional studies to address this question in light of recent trials targeting lipids beyond LDL-C. The ACCORD- lipid arm results (29), and the recently halted AIM-HIGH trial (30) have called into question the value of triglyceride lowering or HDL-C raising strategies in patients who achieve optimal LDL-C goals. These observations re-affirm the need for more intensive LDL lowering. The results of our analyses support the

view that at least a part of the residual CVD risk reduction may require a greater attention to the LDL – particles and Apo-B, beyond LDL-C and non-HDL-C.

A limitation of our study is that we did not have complete assessment of the CVD status and lipid treatment in our cohort, although most of the patients were on statin treatment, given the mean LDL-C of 86 mg/dl. However, we studied a diabetes cohort with a defined range of elevated triglycerides, with the main aim of comparing the concordance and discordance with apo-B in patients who were categorized by the currently defined LDL-C and non-HDL-C goals.

In conclusion, our findings have clinical implications for the management of dyslipidemia in high to very high risk patients with diabetes. Based on our results, we recommend a more informative lipid assessment in such patients to include both non-HDL-C and Apo- B, while we support the need for clinical trials to further refine the targets for both parameters in cardiovascular risk management.

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Figure 1.

Linear regressions between Apo-B and Non-HDL-Cholesterol. Regression slope differences between males and females; $p < 0.05$ by Chi-Square analysis.

Table 1

Distribution of LDL-C, non-HDL-C, and Apo-B according to currently recommended targets in patients with diabetes and no other major CVD risk factors, as defined by ADA/ACC Consensus Statement

	n	Apo-B < 90 mg/dl (%)	Apo-B ≥ 90 mg/dl (%)	Discordance
LDL-C < 100 mg/dl	1083	676 (62.4)	407 (37.6)	+37.6%
LDL-C ≥ 100 mg/dl	347	26 (7.4)	321 (92.6)	-7.4%
Kappa = 0.400				
non-HDL-C < 130 mg/dl	734	607 (82.6)	127 (17.3)	+17.3%
non-HDL-C ≥ 130 mg/dl	696	95 (13.6)	601 (86.4)	-13.6%
Kappa = 0.690				

Table 2

Distribution of LDL-C, non-HDL-C, and Apo-B according to currently recommended targets in patients with known CVD or diabetes plus one or more major CVD risk factors, as defined by by ADA/ACC Consensus Statement

	n	Apo-B < 80 mg/dl (%)	Apo-B ≥ 80 mg/dl (%)	Discordance
LDL-C <70 mg/dl	315	223 (70.8)	92 (29.2)	+ 29.2 %
LDL-C ≥ 70 mg/dl	1115	132 (11.8)	983 (88.2)	-11.8 %
Kappa = 0.564				
non-HDL-C <100 mg/dl	131	123 (62.6)	8 (37.4)	+ 6.1 %
non-HDL-C ≥ 100 mg/dl	1299	232 (17.8)	1067 (82.2)	-17.8 %
Kappa = 0.430				

Table 3

Distribution of LDL-C, non-HDL-C, and Apo-B according to currently recommended targets in patients with very high CVD risk, as defined by NLA Expert Panel

	n	Apo-B < 70 mg/dl (%)	Apo-B ≥ 70 mg/dl (%)	Discordance
LDL-C <70 mg/dl	315	113 (31.5)	202 (64.1)	+ 64.1 %
LDL-C ≥ 70 mg/dl	1115	15 (1.3)	1100	-1.3 %
Kappa = 0.439				
non-HDL-C <100 mg/dl	131	82 (62.6)	49 (37.4)	+ 37.4 %
non-HDL -C ≥ 100 mg/dl	1299	46 (3.5)	1253 (96.5)	-3.5 %
Kappa = 0.597				