Evidence-Based Management of Diabetic Dyslipidemia in a VA Population: Beyond the LDL Target

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Although low-density lipoprotein level has long been considered the primary target in lipid-lowering therapy, these authors also suggest targeting non–high-density lipoprotein level, especially in patients with diabetic dyslipidemia.

Significant progress has been achieved in treating diabetic dyslipidemia in VA patients since the implementation of the VA clinical guidelines, which recommend a low-density lipoprotein (LDL) target level at < 100 mg/dL.[1] Metabolic derangement of lipids in type 2 diabetes is complicated, however, and treatment to LDL target alone does not attenuate cardiovascular events satisfactorily. Current knowledge and research data suggest the need for a multifaceted approach to the management of diabetic dyslipidemia.

Cardiovascular complications are the major cause of morbidity and mortality in patients with type 2 diabetes.[2-3] Diabetic dyslipidemia plays an important role in the development and progression of cardiovascular disease (CVD),[4-6] and is characterized by a decreased high-density lipoprotein (HDL) level, an elevated triglyceride (TG) level, and a normal or elevated LDL level, with smaller and denser particles.[7-10] The association of low HDL level with increased CVD morbidity and mortality has been well recognized in the literature, including in the Framingham heart study.[11] Elevated serum TG level appears to be a marker for other lipoprotein abnormalities, such as increased atherogenic LDL particles and the accumulation of TG-rich lipoproteins (TGRLPs).[12-13]

It is widely accepted that LDL level is the primary target of lipid-lowering therapy in such high risk populations as patients with CVD and diabetes. However, cumulative data have found that a significant percentage of patients with atherosclerotic vascular disease have an LDL level within the optimal range. In addition, some studies have found that patients who received treatment and achieved an LDL level even lower than 70 mg/dL still developed the complications of CVD, which is referred to as residue risk.[14]

There is increasing evidence that elevated TGRLPs, including very low-density lipoproteins (VLDLs) and intermediate-density lipoproteins (IDLs), are important to the pathogenesis of atherosclerosis and its clinical consequences. Although interventional clinical trials are still underway to determine the relationship between elevated TG level and CVD morbidity and mortality in the diabetic population, observational studies have indicated that elevated TG level is associated with increased risk for CVD and mortality.[15-17] Therefore, it is reasonable to target TG level as well as LDL level in lipid-lowering treatment among both the diabetic and general populations. Furthermore, diabetic patients often have elevated TG levels and, because of the limitation of the Friedewald formula, their LDL levels cannot be routinely calculated when their TG values are excessively high. In addition, directly measured LDL values, by themselves, underestimate the cardiovascular risk in the presence of hypertriglyceridemia.

There is a high prevalence of type 2 diabetes in the VA population. Emphasis on aggressive LDL lowering, without targeting TG level, may not be optimal in lipid management. In the VA primary care setting, LDL level < 100 mg/dL is considered the

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Table 1. Patient characteristics		
Characteristic	**Mean or %**	**Range or SD**
Age, y	69.5	31-98
Glycohemoglobin, %	6.95	4.3-15.5
BMI, kg/m^2	31.6	15.3-65
SBP, mm Hg	128	68-227
DBP, mm Hg	68.4	41-119
TC, mg/dL	159.4	38.16
TG, mg/dL	161.4	116.93
LDL, mg/dL	90	31.01
HDL, mg/dL	37.6	11.71
Non–HDL, mg/dL	121.7	29.41
Statin user	68%	–

BMI = body mass index; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride.

Table 2. Classification of patients based on NCEP ATP III guidelines		
Classification	**TG, mg/dL**	**Patients, No. (%)**
Normal	< 150	2,636 (57.8)
Borderline-high	150-199	844 (18.4)
High	200-499	1,001 (21.9)
Very high	≥ 500	87 (1.9)

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; TG = triglyceride.

primary therapeutic target for patients with type 2 diabetes, regardless of TG level. Although the LDL goal attainment has been reached in approximately 70% of patients with type 2 diabetes in our care center, TG reduction has not been as well accomplished. As a consequence, elevated TG level not only may increase the risk of CVD, but also may exaggerate the decrease in LDL level. For example, when evaluating patients with the same total cholesterol (TC) and HDL values, those with higher TG levels will have a lower calculated LDL value, though their risk of CVD complications is much higher.

In addition to LDL goal, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) also places emphasis on targeting other lipid components, such as TGRLPs and HDLs.[18-20] Non–HDL level is recommended as a secondary target by the ATP III, in patients with a TG level above 200 mg/dL. Non–HDL level is considered a surrogate of apolipoprotein B (apoB), the most important atherogenic lipoprotein, and thus can be used to determine the overall CVD risk in patients with diabetic dyslipidemia.[21-23] Furthermore, a simple measurement of non–HDL level—which can be conducted in nonfasting state, regardless of TG level—may be of particular utility since TG level varies with food intake, fasting period, and individual lipid clearance. Several studies have indicated that non–HDL level, instead of LDL level, is a better predictor for vascular inflammation and CVD complications in the diabetic population.[24-27] The ATP III established the goal for non–HDL level in patients with high TG levels at 30 mg/dL higher than that for LDL level, on the premise that a VLDL level of ≤ 30 mg/dL (normal TG level of 150 mg/dL divided by 5) is considered normal.

Considering the high prevalence of diabetes and its morbidity and mortality related to CVD complications among VA patients, we need to redesign the management strategy for diabetic dyslipidemia. A previous survey found that, in patients with type 2 diabetes, there was a higher rate of LDL goal achievement than non–HDL goal achievement because of coexisting hypertriglyceridemia.[28] In order to achieve better clinical outcomes in this patient population, we need to redefine our goals of lipid therapy. The aim of this study, therefore, was to determine the prevalence of hypertriglyceridemia and therapeutic goal achievement of LDL level and non–HDL level in our patients with type 2 diabetes.

METHODS

The VA Central California Health Care System (VACCHCS) is a regional health care center, with annual outpatient visits of about 150,000. Our patient population consists of approximately 50% white, 40% Hispanic, and 10% other ethnicity.

A retrospective medical record review was conducted from the existing electronic records of outpatients who visited the center between January 2006 and December 2007. A search for the *International Classification of Diseases, Ninth Revision*, code for diabetes mellitus yielded a total of 4,568 patients with type 2 diabetes. Clinical data then were collected on demographic characteristics, medications, and relevant laboratory values for this cross-sectional study.

Chemistry and fasting lipids were measured with the Beckman Synchron LX® 200 Analyzer (Beckman Coulter, Inc., Brea, California) per standard protocol in our VACCHCS laboratory, generally after overnight fasting (10 to 12 hours). TC, HDL, and TG levels were measured directly. LDL level was calculated with the Friedewald formula (LDL = TC – HDL – TG/5) if TG values were < 400 mg/dL. LDL level was directly measured if TG values were > 400 mg/dL. Non–HDL level was calculated by the formula: non–HDL = TC – HDL.

The data were analyzed using PASW Statistics 17.0 software (IBM Corporation, Somers, Kentucky). Descriptive data were expressed as percentages, and means with SDs. Patients were grouped based on TG ranges, according to NCEP ATP III classification. For comparison of lipid values, *t* test was performed between the normal TG group and the borderline-high TG group, while analysis of variance with Bonferroni post hoc tests was performed among the 3 groups categorized into high TG levels (borderline-high, high, and very high). We also used McNemar's test to compare lipid goal achievement between LDL level and non–HDL level among the 3 high TG groups. The VA Northern California Institutional Review Board approved the research protocol.

Table 3. Comparison of laboratory values among normal TG and borderline-high TG groups

Laboratory value	Normal TG group	Borderline-high TG group	*P* value
TC, mean, mg/dL	148.60	161.64	< .001
Non–HDL, mean, mg/dL	108.22	126.94	< .001
LDL, mean, mg/d	88.89	92.63	< .001
HDL, mean, mg/dL	40.39	34.70	< .001

HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglyceride.

RESULTS

A total of 4,568 patients with type 2 diabetes (98% male) were included in the study. Patients' characteristics are shown in Table 1. We divided patients into 4 groups based on NCEP ATP III classification of TG ranges (Table 2). Approximately 42% of our diabetic patients had TG levels > 150 mg/dL. There were 2,636 patients (57.8%) in the normal TG group (TG level, < 150 mg/dL), 844 patients (18.4%) in the borderline-high TG group (TG level, 150 mg/dL to 199 mg/dL), 1,001 patients (21.9%) in the high TG group (TG level, 200 mg/dL to 499 mg/dL), and 87 patients (1.9%) in the very high TG group (TG level, ≥ 500 mg/dL).

The mean TC, non–HDL, and LDL levels were significantly higher, and the mean HDL level was significantly lower in the borderline-high TG group, compared with the normal TG group ($P < .001$) (Table 3). However, with progressively elevated TG levels, only the mean TC and non–HDL levels were significantly increased accordingly; calculated LDL levels remained unchanged, as seen in the borderline-high TG and high TG groups (Table 4). In addition, the directly measured mean LDL level in the very high TG group was even lower, compared with the calculated mean LDL levels in the borderline-high TG and high TG groups ($P < .001$).

We also found a significant discrepancy in lipid goal achievement between LDL level and non–HDL level in our diabetic patients with TG levels ≥ 150 mg/dL (Table 5). In the borderline-high TG group, 68% reached the LDL goal of < 100 mg/dL, but only 60% reached the non–HDL goal of < 130 mg/dL. Furthermore, 67.6% of patients in the high TG group achieved an LDL level < 100 mg/dL, but only 35.7% had a non–HDL level < 130 mg/dL; whereas, 86.3% of patients in the very high TG group achieved an LDL level < 100 mg/dL, but only 0.5% reached a non–HDL level < 130 mg/dL.

DISCUSSION

CVD complications associated with type 2 diabetes can lead to significant patient distress, increased use of health care resources, and exces-

Table 4. Comparison of laboratory values among borderline-high TG, high TG, and very high TG groups

Laboratory value	Borderline-high TG group	High TG group	Very high TG group	*P* value
TC, mean, mg/dL	161.64	179.89	223.68	< .001
Non–HDL, mean, mg/dL	126.94	146.36	193.28	< .001
LDL, mean, mg/dL	92.63	92.12	72.39	< .001[a]
HDL, mean, mg/dL	34.70	33.53	30.40	> .05

HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglyceride.
[a]Comparison between directly measured LDL in very high TG group and calculated LDL in borderline-high TG and high TG groups.

Table 5. Comparison of therapeutic goal achievement among borderline-high TG, high TG, and very high TG groups

Therapeutic goal	Patients achieving therapeutic goal, No. (%)		
	Borderline-high TG group	High TG group	Very high TG group
LDL < 100 mg/dL	573 (67.9)	676 (67.6)[a]	75 (86.3)[b]
Non–HDL < 130 mg/dL	507 (60.0)	357 (35.7)	4 (0.5)
P value	< .001	< .001	< .001

HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglyceride.
[a]30 patients' LDL not calculated due to TG > 400 mg/dL. [b]LDL directly measured.

sive costs. Recent studies suggest that tight glycemic control does not reduce CVD event rate and its related mortality.[29-30] Therefore, successful reduction of CVD risk among patients with type 2 diabetes is increasingly dependent on therapeutic strategy targeting multiple major risk factors, especially hypertension and dyslipidemia. Although population-based studies have indicated that LDL level is a major determinant of atherosclerosis in patients with type 2 diabetes, a great deal of additional information is available on abnormal lipoprotein metabolism and its atherosclerotic pathogenesis.

A high serum TG level is associated with other CVD risk factors, including obesity, insulin resistance, diabetes, and low HDL level. Specifically, elevated TG level is associated with TGRLPs (VLDLs and IDLs) and altered LDL particles (higher density, oxidation potential, and glycation).[12-13] Moreover, in the general population, recent evidence further suggests the direct association between elevated TG levels and increased risk of atherosclerotic events.[15-16]

Data from observational studies and interventional clinical trials suggest that apoB level, which reflects all the circulating atherogenic particles, has been found to be more strongly associated with CVD risk than LDL level in both the diabetic and nondiabetic populations.[23-24] Non–HDL level is clinical accepted as a proxy for apoB, and easily determined from the standard lipid profile, requiring no additional expense. On the other hand, calculated LDL level or directly measured LDL level, by themselves, in the presence of hypertriglyceridemia, tend to underestimate the CVD risk. Since TGRLP level is not routinely measured, non–HDL and TG levels may serve as more appropriate and practical lipid treatment targets in diabetic patients.

Our research data are consistent with the NCEP ATP III classification of normal TG level at < 150 mg/dL, because TC, non–HDL, LDL, and HDL values were significantly changed at TG levels above 150 mg/dL. Our clinical data also suggest that either calculated LDL level when TG level is between 150 mg/dL and 399 mg/dL, or directly measured LDL level when TG level is ≥ 400 mg/dL, does not reflect true dyslipidemia status, and may underestimate the risk for CVD complications if the LDL level is considered as the only therapeutic goal. In addition, a low HDL level (< 40 mg/dL) is a categorical risk factor for CVD in patients with type 2 diabetes, especially in patients with mild hypercholesterolemia.[17] This is particularly true in our diabetic population.

The discrepancy between an LDL goal of < 100 mg/dL and a non–HDL goal of < 130 mg/dL became wider

when TG levels were higher. Among the 42% of our diabetic patients with TG levels higher than normal, a significant proportion did not reach the non–HDL target, despite their LDL goal attainment. Therefore, non–HDL level may be superior to LDL level as the lipid target in patients with diabetes and hypertriglyceridemia. In addition, achievement of non–HDL goal of < 130 mg/dL among different TG groups was at 60% in the borderline-high TG group, 35.7% in the high TG group, and only 0.5% in the very high TG group. This suggests that further lowering of TG level may assist in better control of non–HDL level.

In order to improve clinical outcomes with optimal treatment of dyslipidemia in this diabetic population, there is a need to redefine the lipid therapeutic goals that are tailored to diabetic lipid profiles. Lifestyle modification should be emphasized as the primary life-long treatment modality. In addition to lowering LDL level to < 100 mg/dL as the primary lipid goal, it also is prudent to target non–HDL level to < 130 mg/dL in hypertriglyceridemia, which may include TG levels between 150 mg/dL and 200 mg/dL. TG-lowering agents also may be needed as add-on therapy to achieve the TG goal of < 150 mg/dL.

Study limitations

The major strengths of our study are the relatively large sample size and that the lipid analyses were performed in a single central laboratory. In addition, as a retrospective study, it was cost-effective with respect to time and resources. However, data from this cross-sectional study did not evaluate patients' course over time, including information regarding the timing of initiation or duration of lipid-lowering medications, and their effects on lipid profiles, since 68% of those patients were statin users. In addition, our data only reflect a special population of veterans who are predominantly male and elderly. We also were unable to obtain accurate information on ethnic background because of incomplete data. Therefore, our study findings should be interpreted with caution and should not lead to generalization or causality.

Our data suggest the use of non–HDL level as one of the major lipid treatment targets in patients with hypertriglyceridemia. Prospective studies in the general population are warranted to further evaluate the effect of non–HDL target achievement on cardiovascular outcomes.

CONCLUSION

The study findings demonstrated a high prevalence of hypertriglyceridemia in our diabetic population. A significant proportion of our diabetic patients with calculated or directly measured LDL level targeted at < 100 mg/dL still did not meet the non–HDL treatment goal of < 130 mg/dL. In order to further improve cardiovascular outcomes in our type 2 diabetic population, we need to adopt the NCEP ATP III guideline to target non–HDL level at < 130 mg/dL in those patients with TG levels ≥ 200 mg/dL. We should continue to use LDL level < 100 mg/dL as the primary lipid therapeutic target for patients with TG levels < 200 mg/dL. We may consider TG level < 150 mg/dL as a secondary lipid goal in patients with TG levels > 150 mg/dL.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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