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# Diabetic dyslipidemia

## *Dislipidemia diabética*

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In 2015, it was estimated that there were 415 million (uncertainty interval: 340-536 million) people aged 20-79 with type 2 diabetes mellitus (DM2), 5 million deaths attributable to DM2, and the total global health expenditure due to diabetes were 673 billion U.S. dollars. Three-quarters (75%) of those with DM2 were living in low and middle-income countries. The number of patients with diabetes (20-79 years old) will rise to 642 million by 2040.[1] Because of this, diabetes prevalence, deaths attributable to diabetes, and health expenditure due to diabetes have continued to grow across the world with important social, financial, and health system implications.

### ROLE OF DIABETES MELLITUS DYSLIPIDEMIA

Many patients with DM2 have dyslipidemia, which is essential in the rising of cardiovascular (CV) risk. Lipids and glucose play a crucial role in energy metabolism. It is well known that patients with diabetes often have dyslipidemia, characterized by increased triglycerides, low high-density lipoprotein cholesterol (HDL-c), a predominance of small-dense low-density lipoprotein (LDL) particles, and higher concentrations of apoB-containing particles.[2-4]

However, recent research indicates that lipid changes may not be the only consequence of diabetes since they may also cause disturbances in glucose metabolism. Lipid changes are observed in insulin-resistant persons with normal glucose tolerance and in those with metabolic syndrome years before the clinical diagnosis of DM2 occurs.[5] This suggests either co-associations of independent disorders or a pathophysiologic role for insulin resistance, rather than hyperglycemia itself, in the development of diabetic dyslipidemia.

Although not all patients with diabetes show all manifestations, 60 to 70% of them, present some lipid abnormalities.[6] Dyslipidemia is a major and probably the most critical link between diabetes and CV disease. However, hyperglycemia accelerates atheroma formation in the setting of diabetic dyslipidemia.

The metabolism of very-low-density lipoprotein (VLDL), the primary transporter of fasting triglycerides, is insulin-regulated at multiple levels. Insulin suppresses lipolysis and regulates circulating free fatty acids, which are substrates for VLDL cholesterol assembly and secretion. In the liver, insulin mediates the transfer of triglycerides to apoB and regulates lipoprotein lipase (LPL) activity to delipidate VLDL. LPL activity can be disrupted by increased circulating free fatty acids and inhibited by apoC III. In contrast, apoC III hinders hepatic uptake of triglyceride-rich lipoproteins and is itself inhibited by insulin. Thus, in the insulin-resistant state, hypertriglyceridemia may result from elevated free fatty acid levels and decreased degradation of apoB, leading to over-production of VLDL, impaired lipoprotein lipase activity, and decreased hepatic uptake of VLDL with reduced VLDL clearance.

Increased free fatty acids (FFA) impair insulin signaling and cause subclinical inflammation with subsequent pancreatic β-cell dysfunction. FFA increase may be involved in the induction of a pro-thrombotic state. Interestingly, increased concentration of triglyceride-rich lipoproteins leads to increased catabolism of HDL, lowering its plasma concentration.

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In contrast, triglyceride-enriched LDL particles undergo hydrolysis, decreasing particle size and shifting the LDL phenotype towards small and dense LDL, which are more atherogenic than «normal» LDL. As such, lipid changes may not only be a consequence of impaired glucose metabolism, but they may also cause it. Seems that elevated concentrations of FFA disrupt or modulate the cascade linking insulin receptors with glucose transporters and impair the normal function of the β-cell. Hypertriglyceridemia (HTG) may induce subclinical inflammation, which then leads to insulin resistance and β-cell dysfunction. These lipid changes are seen in patients with overt diabetes and patients with metabolic syndrome and obesity, and they reflect insulin resistance rather than hyperglycemia. HTG can worsen glucose metabolism. This fact explains why it is more challenging to control hyperglycemia in patients with HTG than those with normal triglyceride values. It also explains why patients usually require less intensive antidiabetic treatment once their hypertriglyceridemia has been resolved. Mechanisms underlying diabetic dyslipidemia remain incompletely understood.

## LIPID-LOWERING THERAPY: STATINS IN DIABETES MELLITUS

Strong evidence showing that lipid-lowering therapy with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-Co-A) reductase inhibitors (statins) reduces ASCVD event rates in diabetes mellitus is available from clinical trials.

Some statin's benefits are potentially attributable to nonlipid-lowering related anti-inflammatory effects. The 2016 guidelines from the American College of Cardiology/American Heart Association recognize the patients with diabetes mellitus (ages 40 to 75 years ) as one of the four principal groups to benefit from statins and recommend treatment with a moderate-intensity statin or a high-intensity statin for individuals with a ≥ 7.5% 10-year risk of cardiovascular disease.[7] In subjects under 40 or over 75 years of age, guidelines recommend individualizing statin therapy based on benefits of ASCVD risk reduction versus the potential for adverse effects, the interactions with other drugs, and patient preference. Statin-induced lowering of LDL cholesterol levels by 39 mg/dL (1 mmol/L) in high-risk individuals reduces coronary mortality risk by 19%, as demonstrated in a meta-analysis by the Cholesterol Treatment Trialists' Collaboration. The magnitude of mortality benefits was similar for those with or without diabetes mellitus.[7] A 21% reduction in major vascular events occurred per 1-mmol/L reduction in LDL cholesterol, irrespective of prior history of vascular disease, gender, age, body mass index (BMI), baseline systolic or diastolic blood pressure, smoking status, estimated glomerular filtration rate, cholesterol, or predicted annual risk of major vascular events. The collaborative atorvastatin diabetes study (CARDS) trial specifically assessed 2,838 patients DM2, including patients with a mean baseline LDL-c level of 117 mg/dL (3.0 mmol/L) randomized to atorvastatin 10 mg daily or placebo. Results of this trial show a 37% reduction in the primary cardiovascular composite outcome (time to first occurrence of acute coronary heart disease event, coronary revascularization, or stroke). The treating to new targets (TNT) study examined whether lowering LDL cholesterol below the threshold recommended at the time (100 mg/dL, 2.59 mmol/L) would result in more significant cardiovascular risk reduction. For that reason, 1,501 patients with diabetes mellitus and coronary artery disease (CAD) were randomized to atorvastatin 10 mg versus 80 mg daily. Treatment decreased LDL-c levels to a mean of 98.6 mg/dL (2.55 mmol/L) versus 77 mg/dL (1.99 mmol/L), respectively. There was also a 25% reduction in major cardiovascular events after 4.9 years of treatment. This study provides further evidence that more aggressive LDL-lowering reduces ASCVD in diabetes mellitus.

## NON-STATIN LIPID-LOWERING

Despite the reduced risk of ASCVD with statin therapy, a residual risk remains for diabetic and non-diabetic patients, and further lowering of lipids may be of value. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) supports the use of a combination of simvastatin and ezetimibe, a nonstatin LDL-lowering

molecule (which reduces intestinal cholesterol absorption) to further lower cardiovascular risk. The primary composite cardiovascular endpoint of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke was 6% lower comparing ezetimibe with placebo administered with simvastatin, with a greater 14% cardiovascular benefit among those with diabetes mellitus.

## PHARMACOLOGIC INTERVENTIONS TO MODIFY HYPERTRIGLYCERIDEMIA AND LOWER DL LEVELS HAVE NOT SHOWN A CLEAR REDUCTION IN CLINICAL HARDPOINTS

Targeting the diabetic lipid abnormalities; increased triglycerides, low HDL cholesterol, and small LDL cholesterol particle size will further benefit remains as a relevant question. Recent trials, as the lipid arms of action to control cardiovascular risk in diabetes (ACCORD) and the fenofibrate intervention and event lowering in diabetes (FIELD), examined fenofibrate effects. In the ACCORD trial, all patients were randomized to intensive glycemic control, and a subset of patients was enrolled in the ACCORD Lipid trial to receive simvastatin plus fenofibrate or placebo. Although there was no difference in the annual rate of primary composite outcomes of major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) for the fenofibrate in comparison with placebo group, subgroup analysis revealed 29% fewer events in those with baseline triglyceride ≥ 204 mg/dL (2.31 mmol/L) and HDL cholesterol ≤ 34 mg/dL (0.88 mmol/L). These results are consistent with the FIELD study in 9,975 individuals with DM2 not under statin therapy. No effect of fenofibrate was observed on the primary outcome of coronary events (coronary heart disease death or nonfatal myocardial infarction) in the entire cohort. However, a 14% cardiovascular event reduction in the subgroup with low cholesterol linked to high density lipoproteins (HDL-c) at baseline ($p = 0.02$) and a similar trend in those with HTG at baseline ($p = 0.07$) was observed.

In the atherothrombosis intervention in metabolic syndrome with low HDL/high triglycerides and impact on global health outcomes (AIM-HIGH), a study that evaluated the addition of niacin to intensive statin therapy (simvastatin plus ezetimibe if needed to maintain LDL concentrations of 40-80 mg/dL [1.04-2.07 mmol/L]) in patients with established cardiovascular disease and low HDL-c (median baseline of 35 mg/dL [0.91 mmol/L]), where approximately one-third of participants had diabetes mellitus, no difference in the primary composite endpoint was observed despite increasing HDL-c concentration from 35 to 42 mg/dL (0.91-1.09 mmol/L), lowering triglycerides from 164 to 122 mg/dL (1.85 to 1.38 mmol/L), and lowering LDL-c from 74 to 62 mg/dL (1.92 to 1.61 mmol/L).

Consideration can also be given to adding fibrate therapy for an individual with DM2 and residual HTG with low c-HDL levels, once the patient is on goals with statin therapy. In this context, ezetimibe may represent a reasonable choice for additional cardiovascular risk reduction, especially in those patients with DM2 and acute coronary syndrome. This is consistent with the most recent Standards of Medical Care for Diabetes by the American Diabetes Association (ADA),[8] which cite a level A evidence showing that the addition of ezetimibe to moderate-intensity statin therapy may be considered for patients with a recent acute coronary syndrome with LDL cholesterol ≥ 50 mg/dL (1.3 mmol/L) or for those patients who cannot tolerate high intensity statin therapy.

The 2019 European Society of Cardiology (ESC) Guidelines for the management of dyslipidemias,[9] suggest that if treatment goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended. The combination therapy with a statin and fibrate has not been shown to improve ASCVD outcomes in the broad diabetes mellitus population and is generally not recommended. Of note, the Scientific Statement on Prevention of Cardiovascular Disease in type 2 diabetes mellitus by the American Heart Association and American Diabetes Association (AHA/ADA) does not recommend the addition of a fibrate to statin therapy.

There is limited data on the impact of adding omega-3 fatty acids to statin therapy in patients with high plasma triglyceride

levels treated with statins. The REDUCE-IT trial examined the effects of icosapent ethyl 2 g b.i.d. on CV events in 8,179 high-risk patients with HTG under a statin therapy. Over a median of 4.9 years, a significant ($p < 0.001$) 25% reduction in the composite primary outcome of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina.

## LDL-LOWERING WITH PCSK9 INHIBITION

The newest class of c-LDL-lowering formulations are monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 inhibitors prevent the degradation of LDL-c receptors, allowing for increased removal of LDL-c from the circulation. Alirocumab and evolocumab are 2 PCSK9 inhibitors recently approved by the Food and Drug Administration (FDA). Alirocumab was approved for use alongside diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia or patients with clinical ASCVD who require additional lowering of LDL-c. A *post hoc* analysis of the effect of alirocumab on cardiovascular outcomes was performed in the long-term safety and tolerability of alirocumab in high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their lipid modifying therapy (ODYSSEY LONG TERM) trial showed a 48% reduction in major adverse cardiovascular events ($p = 0.02$). The cardiovascular outcome trial FOURIER[10] (the further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk), was a placebo-controlled trial involving 27,564 patients with ASCVD and LDL-c concentrations of 70 mg/dL (1.8 mmol/L) or higher who received statin therapy, with a primary efficacy endpoint composed by CV death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. At 48 weeks, the percentual reduction in LD-cL concentrations with evolocumab, was 59%, from 92 mg /dL (2.4 mmol/L) to 30 mg/dL (0.78 mmol per liter) ($p < 0.001$). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary endpoint (1,344 patients [9.8%] vs 1,563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; $p < 0.001$) and the key secondary endpoint (816 [5.9%] vs 1,013 [7.4%]; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; $p < 0.001$). These findings show inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL-c to a median of 30 mg /dL (0.78 mmol/L) and reduced the risk of CV events.

This evidence shows that the strategy and primary objective of treating dyslipidemia in both non-diabetic and diabetic patients are to achieve the LDL-c goals determined by each patient's risk. This goal is < 55 mg/dL in very high-risk diabetic or non-diabetic patients with additional cardiovascular risk factors or ASCVD. The goal is < 70 mg/dL in high risk diabetic or non-diabetic patients and < 100 mg/dL in diabetic or non-diabetic patients with moderate risk.

## CONCLUSIONS

Diabetes mellitus and dyslipidemia commonly occur together, with lipid abnormalities affecting 60% to 70% of patients with DM2 and hyperglycemia accelerates atheroma formation in the setting of diabetic dyslipidemia. Dyslipidemia is crucial in mediating the CV risk in diabetes. HTG and low c-HDL may also induce glucose metabolism disturbances and may thus be the consequence and the source of hyperglycemia. Diabetes mellitus exacerbates the mechanisms of atherosclerosis. Aggressive management of CV risk factors, particularly lowering of LDL-c concentration, provides substantial prevention of CV outcomes. The role of new potent lipid-lowering therapies (PCSK9 inhibitors) and lipid-lowering drugs that target triglycerides and HDL-c needs further studies. Although the overall management of diabetes mellitus has improved substantially over the past two decades, there is a significant unmet need for cardiovascular prevention.

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