

Dyslipidemia In Diabetic Patients



Diabetes is an emerging epidemic in Canada. Aggressive management of dyslipidemia and associated risk factors is essential to minimize the morbidity and mortality of these patients.

By Robert C. Welsh, MD, FRCPC; and Troy D. Schultz, BSc

Diabetes mellitus (DM) is an emerging epidemic with 2.2 million Canadians currently diagnosed, 60,000 new cases found each year and three million patients projected by the year 2010. It is frequently devastating, with both acute

and chronic complications, including microvascular and macrovascular arterial disease. The treatment of insulin-dependent DM, non-insulin-dependent DM and management of associated medical complications represents annual medical costs in Canada totalling \$9 billion.

The metabolic milieu of DM poses an extremely potent atherosclerotic stimulus and it is a major risk factor for cerebrovascular, peripheral vascular and cardiovascular disease. An alarming 80% of deaths in diabetic patients are related to atherosclerotic complications, compared to approximately 40% in the general population. This metabolic syndrome is associated with multiple classical cardiac risk factors (dyslipidemia, hypertension) and a number of novel markers of risk (Lipoprotein a [Lp(a)], hyperhomocysteine).

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Case

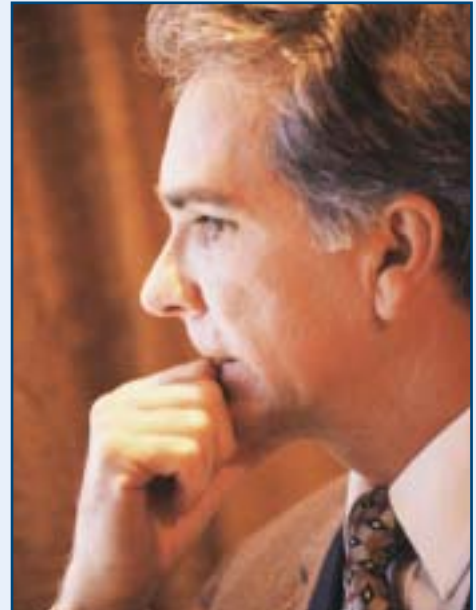
Mr. Smith, 42, has recently moved to your community and has come to your office for a medical followup. He was diagnosed with diabetes mellitus at the age of 27 and has diabetic retinopathy treated with laser surgery.

The remainder of his past medical history includes: mild hypertension for which he takes ramipril, 2.5 mg daily, a previous cigarette-smoking habit (he quit 10 years ago), a family history of coronary artery disease (father age 54) and he is unaware of his lipid status. He currently takes insulin twice daily.

Physical examination shows a mildly obese man with a blood pressure (BP) of 138/88 mmHg, heart rate of 76 bpm and a respiratory rate of 14. Jugular venous pressure was not elevated and there was no peripheral edema. The carotid contour and upstroke appeared normal with no audible carotid bruits, and peripheral pulses were palpable and not diminished. The apical impulse was within normal limits, first and second heart sounds were normal, with an I/VI systolic murmur best heard at the right upper sternal edge with no radiation.

His 12-lead electrocardiogram and chest X-ray were interpreted as normal. Complete blood count, electrolytes, urea and creatinine were normal with a glycosylated hemoglobin A (HbA1c) of 7.9. Lipid profile shows total cholesterol of 5.6 mmol/L, LDL-C of 3.2 mmol/L, HDL-C of 0.9 mmol/L and triglycerides of 3.1 mmol/L.

Question: *At this stage, what are appropriate further investigations and therapy for Mr. Smith?*



Although LDL-C reduction should remain the focus of therapy in dyslipidemia, appropriate therapy for low HDL-C should also be considered.

Undoubtedly, there are further abnormalities yet to be defined. Aggressive management of DM and associated risk factors is essential to minimize the morbidity and mortality of these patients. Unfortunately, a major treatment gap exists in the management of dyslipidemia, with only 30% of patients on medical therapy and many not achieving target levels.¹

This article will review DM focusing on dyslipidemia (low-density lipoprotein [LDL-C], high-density lipoprotein [HDL-C], triglycerides [TG]), novel markers of risk (Lp(a) and homocysteine), and current treatment recommendations.

Dyslipidemia in Diabetics

LDL-C: Multiple observational studies have documented the direct correlation of hypercholesterolemia and increased risk of atherosclerotic disease. Over 30,000 patients assessed in randomized trials with HMG Co-A reductase inhibitors (statins) have demonstrated consistent reduction in cardiovascular events in diverse patient populations. Although specific randomized trials

in DM are sparse, evidence suggests direct correlation of LDL-C reduction and cardiac events in essentially every patient subgroup, with the largest absolute benefit achieved in patients with the highest risk.

It has been demonstrated consistently that DM patients are at very high risk, with asymptomatic diabetics having a ten-year cardiovascular risk similar to that of non-diabetics with documented ischemic heart disease. In addition to dyslipidemia, aberrations in the composition of the LDL-C molecule further increase the risk of vascular disease in diabetics. Such alterations include glycation, oxidation and altered lipoprotein composition, such as small, dense LDL-C, apolipoprotein B (apo-B) and TG-enriched LDL-C. Subgroup analysis of DM patients has demonstrated consistent benefit from LDL-C reduction, with reduced risk of major cardiac events of a similar or greater magnitude than non-diabetic patients (Table 1). The Canadian Working Group on Hypercholesterolemia has recommended aggressive screening and treatment of hypercholesterolemia in DM, with all patients > 30 years of age considered to be at very high risk (Table 2).²

HDL-C: It has long been known that the atherogenicity of dyslipidemia is not isolated to LDL-C, but also related to low HDL-C, which is a powerful independent predictor of coronary heart disease.³ In fact, the most efficient lipid profile for predicting coronary disease in the Framingham Study was shown to be the total cholesterol to HDL-C ratio, which is supported by other epidemiologic studies. The HDL-C particle is protective, since it promotes the esterification and transfer of cholesterol from peripheral cells to the hepatic cells for metabolism in the liver.

Table 1

Major Randomized Trials with Diabetic Subgroup Analysis

Study	Agent	Total patients	ARR	NNT
4S	Simvastatin	4,444	-3.6%	12
CARE	Pravastatin	4,159	-0.8%	33
LIPID	Pravastatin	9,014	-3.1%	28
VA-HIT	Gemfibrozil	2,531		23

Diabetic Subgroup

Study	Agent	DM patients	ARR	NNT
4S	Simvastatin	483	-14.0%	7
CARE/LIPID	Pravastatin	1,368	-3.5%	29
VA-HIT	Gemfibrozil	769	-8.2%	12

NNT = Number Needed to Treat

ARR = Absolute Risk Reduction

Retrospective analysis of major statin trials demonstrated a “remaining” risk of low HDL-C, even with statin therapy. Furthermore, the statins have various effects on HDL-C, depending on baseline levels, specific agent and dosage. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study (VA-HIT) demonstrated relatively minor increases in HDL-C, and reductions in TG with gemfibrozil were associated with reduced cardiovascular events of a magnitude similar to past statin trials. This benefit appeared consistent in DM (Table 1).⁴ Although LDL-C reduction should be the focus of dyslipidemia therapy, appropriate therapy for low HDL-C should also be considered.

TG: Elevation of plasma TG is one of the most consistent abnormalities associated with DM, and plasma levels of LDL-C are strongly correlated with plasma TG levels.

The relationship of elevated TG to atherosclerosis has been partially obscured by this interrelationship, but despite these interactions, the weight of evidence supports TG as an independent risk factor especially in DM. As plasma TG levels rise, the relative proportion of cholesterol ester transferred from HDL-C to very low-density lipoprotein cholesterol (VLDL-C) increases, which explains the increased number of small, dense VLDL-C particles found in DM. TG-enriched lipoproteins are relatively smaller in size and can more easily enter the vessel walls where they are oxidized and accelerate the atherosclerotic process. Furthermore, once the HDL-C molecule becomes TG-enriched, it is taken up by the liver, resulting in a decline in HDL-C levels through hepatic metabolism.

Table 2

CAD Risk Classification for DM Patients

Patients with diabetes mellitus over the age of 30 are now classified as being at a very high risk for CAD.

Level of risk	LDL-C mmol/L	TC: HDL-C Ratio mmol/L	TG mmol/L	Treatment
Very High (10-year risk > 30%, or or history of CV disease or diabetes)	< 2.5	< 4	< 2.0	Start medication and lifestyle changes concomitantly if values are above target values.
High (10-year risk 20-30%)	< 3.0	< 5	< 2.0	
Moderate (10-year risk 10-20%)	< 4.0	< 6	< 2.0	Start medications if target is not achieved after 3 months of lifestyle modifications.
Low (10-year risk < 10%)	< 5.0	< 7	< 3.0	Start medications if target is not achieved after 6 months of lifestyle modifications.

LDL-C = Low Density Lipoprotein
HDL-C = High-Density Lipoprotein
TC = Total Cholesterol

TG = Triglyceride
CAD = Coronary Artery Disease
CV = Cardiovascular

Adapted from: Fodor JG, Frohlich JJ, Genest JJ, Jr., et al: Recommendations for the management and treatment of dyslipidemia. Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. CMAJ 2000; 162(10):1441-47.

Emerging Markers of Cardiovascular Risk in Diabetes Mellitus

Emerging hematologic and biochemical markers for cardiovascular disease are currently under investigation and further research will clarify their potential for clinical use and the impact on management of

patients, including those with DM. Although there are multiple markers currently under investigation, the following discussion will be limited to Lp(a) and homocysteine as they relate to DM.

Lp(a): Numerous epidemiologic studies have indicated that elevated plasma Lp(a) is an independent risk factor for atherosclerosis in patient populations including DM.⁵

Lp(a) has been demonstrated to enhance cell repair, strengthen the extra-cellular matrix, and prevent lipid peroxidation, but deregulation of this “normal” process could initiate or promote atherosclerosis.⁶ It has been proposed that the molecular homology of Lp(a) to plasminogen with impaired endogenous fibrinolysis by competitive inhibition of plasminogen on the vascular endothelial surface may represent another mechanism of atherogenicity.⁷ Altered renal function may also contribute to altered Lp(a) in DM patients (both Type 1 and Type 2) since microalbuminuria, macroalbuminuria and renal failure are correlated with elevated levels.⁸ Since diabetes is the most common cause of end-stage renal disease and chronic dialysis, these interactions need to be studied further.

Treatment of dyslipidemia impacts Lp(a) since it is directly correlated with LDL-C and negatively correlated with TG levels in diabetic patients.⁹ Thus, statins may indirectly lower Lp(a) levels and further decrease the cardiovascular risk profile. Although clinical end point data is clearly required before therapy can be recommended, in patients with Lp(a) elevation, the use of niacin and ascorbate acid has been associated with reduced levels.⁶

Homocysteine: Recent studies have demonstrated a significant relationship between plasma homocysteine levels and atherosclerotic risk. This is of particular importance in DM patients who frequently have elevated levels of homocysteine and it appears to be a stronger cardiovascular risk factor for these patients, than in subjects with normal glucose tolerance.¹⁰ Homocysteine, as a thrombogenic agent, can cause endothelial injury, promote vascular smooth muscle cell growth, inhibit endothelial cell growth, and modify



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endothelial cell coagulant properties. Declining renal function is associated with higher plasma homocysteine levels and patients with end-stage renal disease usually exhibit homocysteine levels that are at

Case Discussion

This patient has a 15-year history of diabetes mellitus with evidence of diabetic retinopathy, mild hypertension on low-dose ACE inhibitor and the typical dyslipidemia of a diabetic. Although he does not have a clinical history suspicious for ischemic heart disease, evidence suggests that he is high risk due to the fact that he is a diabetic with several risk factors (family history, hypertension, past cigarette smoker and mild dyslipidemia).

Appropriate investigations and management for this patient include: maximal control of hypertension and DM with further assessment of renal function. Although his lipid profile is only mildly "abnormal," it does not meet the goal levels outlined in the Canadian Working Group on Dyslipidemia guidelines. Therefore, appropriate pharmacologic therapy, as well as lifestyle changes, should be implemented at this time.

The patient was started on simvastatin, 20 mg, his ramipril dosage was increased to 10 mg, and he was referred to a multifaceted diabetes clinic.

least three times the upper normal value.¹¹ Current research attempting to demonstrate clinical efficacy of lowering homocysteine is underway and recommendations for specific medical intervention are forthcoming.

Current Clinical Implications

DM requires comprehensive assessment and management, including lifestyle (diet and exercise) and pharmacologic interventions. Although direct randomized clinical end-point trials are limited, diabetics are the highest risk patient group for cardiovascular disease and expert consensus recommends aggressive assessment and management of dyslipidemia. The impact of the expanding list of novel markers of cardiovascular risk in DM and other patient populations requires further research to clarify their clinical utility. The aim when treating dyslipidemia in DM should be to achieve the goals outlined by the Working Group on

Hypercholesterolemia and Other Dyslipidemias (LDL-C < 2.5 mmol/L, TC:HDL-C ratio < 4, and TG < 2.0 mmol/L). The magnitude of evidence clearly resides with statins, which should be considered first-line therapy, although data concerning fibrates show benefit in appropriate patients (low LDL-C, elevated TG and decreased HDL-C). Combination therapy may be required in DM and, if initiated, clinical vigilance for complications related to medication side effects and drug interactions is essential. Current recommendations for pharmaceutical intervention for dyslipidemia are outlined by the Working Group on Hypercholesterolemia and Other Dyslipidemias (Table 3).²

Future Clinical Implications

The recommendations for management of dyslipidemia are currently under revision to incorporate the evidence from the Heart

Protection Study (HPS) (presented, not yet published). HPS provides further evidence of the importance of LDL-C lowering in a broad group of patients with consistent benefits in subgroup analysis, including those with low LDL-C levels prior to therapy. The results of this trial and the Treatment to Targets study may significantly alter the current guidelines. HPS will also greatly enhance the current knowledge of statin treatment in DM patients (5,963 DM/20,536 total enrolled) and preliminary results suggest consistent risk reduction.

With the increasing prevalence of DM and associated complications, such as renal insufficiency/failure, which further increase cardiovascular risk, further research is required to assess the impact of novel approaches to management in this complex group. Renal, pancreas and islet cell transplantation have the potential to improve patients' quality of life and long-term outcomes, but potential interactions with the required immunosuppressive agents may accelerate atherosclerosis or lead to drug interactions. Furthermore, appropriate cardiac risk stratification prior to clearance for transplantation has not been studied appropriately.

In conclusion, diabetic patients represent the highest risk groups for cardiovascular disease and the management of dyslipidemia in this group has to be promoted and maximized. In an era of multifaceted diabetic clinics that promote thorough assessment, management and education, appropriate referral

of this complex group of patients should be encouraged. 

Table 3

Therapy of Choice for Different Lipid Profiles

Lipid Profile	Agent
Elevated LDL-C Alone With moderate TG With low HDL-C	Statin Statin with or without resin Combination therapy may be required (statin +/- fibrate or niacin)
Normal LDL-C Elevated TG Low HDL-C	Niacin or fibrate or combination Niacin or fibrate or combination

LDL-C = Low Density Lipoprotein

TG = Triglycerides

HDL-C = High Density Lipoprotein

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Dyslipidemia in Diabetics

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