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### Lipids and lipid management in diabetes



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Cardiovascular disease is more prevalent in type 1 and type 2 diabetes, and continues to be the leading cause of death among adults with diabetes. Although atherosclerotic vascular disease has a multi-factorial etiology, disorders of lipid metabolism play a central role. The coexistence of diabetes with other risk factors, in particular with dyslipidemia, further increases cardiovascular disease risk. A characteristic pattern, termed diabetic dyslipidemia, consists of increased levels of triglycerides, low levels of high density lipoprotein cholesterol, and postprandial lipemia, and is mostly seen in patients with type 2 diabetes or metabolic syndrome.

This review summarizes the trends in the prevalence of lipid disorders in diabetes, advances in the mechanisms contributing to diabetic dyslipidemia, and current evidence regarding appropriate therapeutic recommendations.

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#### Introduction

Diabetes mellitus contributes substantially to the global burden of disease, with an estimated 366 million people affected worldwide, and expected to increase to 552 million by 2030 [1].

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Cardiovascular disease (CVD) is more prevalent in patients with diabetes and is the leading cause of death among adults with diabetes [2,3]. Atherosclerotic vascular disease has a multi-factorial etiology that includes hypertension, hyperlipidemia, diabetes, obesity, chronic inflammation, sedentary lifestyle and cigarettes smoking [4]. In the absence of diabetes, disorders of lipid metabolism play a central role in atherogenesis and its progression [5,6]. In the Multiple Risk Factor Intervention Trial (MRFIT) study, among 340,000 middle-aged Americans, 1 mmol/L lower total cholesterol was associated with approximately 50% lower coronary disease risk [7]. Similar observations were reported in the Framingham cohort [8].

It had been shown that the presence of diabetes confers an enhanced CVD risk when compared with other traditional risk factors, in particular the association with dyslipidemia [9]. Patients with diabetes, especially type 2 diabetes (T2D), have an increased prevalence of lipid abnormalities, contributing to their high risk of CVD. More recent studies have reported that the prevalence of lipid disorders is much higher in children and youth with diabetes [10].

Multiple clinical trials have demonstrated favorable effects of pharmacologic (primarily statin) therapy on CVD outcomes in subjects with coronary heart disease (CHD) and for primary CVD prevention. Other classes of lipid lowering medication have shown less consistent effects on cardiovascular outcomes, in spite of their effectiveness on lipid levels.

This review summarizes the trends in the prevalence of lipid disorders in diabetes, advances in the mechanisms contributing to diabetic dyslipidemia, and current evidence regarding appropriate therapeutic recommendations.

### Patterns and prevalence of dyslipidemia in diabetes

Although the prevalence of dyslipidemia is higher in T2D, various abnormalities of lipoprotein metabolism may also occur in individuals with type 1 diabetes (T1D) [11].

Patients with poorly controlled T1D present with elevated levels of triglyceride (TG)-rich lipoproteins [very low density lipoproteins (VLDL) and chylomicrons] due to a reduction in the activity of lipoprotein lipase (LPL) in the muscle and adipocytes [12]. This increase in TG-rich lipoproteins promotes an increased exchange of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesteryl esters for TG in chylomicrons and VLDL, which in turn reduces HDL-C levels and generates small, dense LDL [12]. Insulin deficiency is also associated with an increase in the absolute levels of LDL-C, LDL particle number, and apolipoprotein B-100, because LDL receptor expression is regulated, in part, by insulin. In contrast, patients who have well-controlled T1D have serum lipids and lipoprotein levels that are similar to those in the general population [11]. It has been reported that even when the absolute levels of plasma lipid and lipoprotein are normal, the apolipoprotein (apo) B-lipoproteins are cholesteryl ester-enriched and potentially more atherogenic [12]. In addition, the current weight trends in individuals with T1D, show an increased prevalence of obesity, metabolic syndrome [13,14], and as a consequence insulin resistance. These T1D individuals may present with dyslipidemia that resembles the characteristic abnormalities seen in patients who have T2D.

Most patients with T2D present with a cluster of lipoprotein abnormalities that include elevated fasting and postprandial TG levels, and decreased HDL-cholesterol levels. The levels of total and LDL-cholesterol are usually not significantly different in T2D patients compared with nondiabetic individuals, although some studies have reported that women with T2D may have a modest increase in LDL-cholesterol [15]. In the Framingham Heart Study, 13% of men and 24% of women with diabetes had increased total plasma cholesterol levels, compared with 14% of men and 21% of women without diabetes, while the prevalence of high LDL-cholesterol levels was 9% and 15%, respectively in men and women with diabetes mellitus compared with 11% and 16%, respectively in non-diabetic men and women [16]. The prevalence of high plasma TG levels (defined in this study as  $\geq 2.65$  mmol/L or 234.7 mg/dl) (19% men; 17% in women), and low HDL-cholesterol level (defined as  $\leq 0.8$  mmol/L or 30.93 mg/dl) (21% men and 25% women), were however significantly higher in individuals with diabetes than in those without diabetes (9% of men; 8% of women, and 12% men; 10% women, respectively) [16].

In spite of relatively normal absolute LDL-cholesterol levels, individuals with T2D usually present with an increase in the smaller, and more dense LDL particles. An increase in small LDL particle

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