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Reviews

Diabetic dyslipidemia

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ABSTRACT

Diabetic dyslipidemia is characterized by elevated fasting and postprandial triglycerides, low HDL-cholesterol, elevated LDL-cholesterol and the predominance of small dense LDL particles. These lipid changes represent the major link between diabetes and the increased cardiovascular risk of diabetic patients. The underlying pathophysiology is only partially understood. Alterations of insulin sensitive pathways, increased concentrations of free fatty acids and low grade inflammation all play a role and result in an overproduction and decreased catabolism of triglyceride rich lipoproteins of intestinal and hepatic origin. The observed changes in HDL and LDL are mostly sequence to this. Lifestyle modification and glucose control may improve the lipid profile but statin therapy mediates the biggest benefit with respect to cardiovascular risk reduction. Therefore most diabetic patients should receive statin therapy. The role of other lipid lowering drugs, such as ezetimibe, fibrates, omega-3 fatty acids, niacin and bile acid sequestrants is less well defined as they are characterized by largely negative outcome trials. This review examines the pathophysiology of diabetic dyslipidemia and its relationship to cardiovascular diseases. Management approaches will also be discussed.

1. Introduction

Diabetes is a well-established independent risk factor for cardiovascular diseases (CVD). Compared with non-diabetic individuals, diabetic patients have 2 to 4 times increased risk for stroke and death from heart disease [1]. Hyperglycemia cannot entirely account for the high cardiovascular risk in diabetic patients. In fact, aggressive glycemic control does not necessarily lead to a substantial reduction in cardiovascular events or mortality [2]. In recent decades, strategies for managing vascular complications associated with diabetes have moved away from a "glucocentric" approach to address additional risk factors that contribute to the development and progression of atherosclerosis. A very common metabolic abnormality associated with diabetes is dyslipidemia, which is characterized by a spectrum of quantitative and qualitative changes in lipids and lipoproteins. A common pattern of lipid abnormalities, known as diabetic dyslipidemia, includes hypertriglyceridemia, reduced high-density lipoprotein (HDL)-cholesterol concentration and a shift towards small dense low-density lipoprotein (LDL) [3]. In this review, we summarize the pathophysiology of diabetic dyslipidemia and address the potential role of dyslipidemia in causing type-2 diabetes. Effects of the individual lipid components on CVD will also be

Abbreviations: ABCA1, ATP-binding cassette transporter, subfamily A, member 1; ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; apoA1, apolipoprotein A1; apoB, apolipoprotein B; apoCIII, apolipoprotein CIII; BAS, bile acid sequestrants; BMI, body mass index; CETP, cholesteryl ester transfer protein HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment estimate of insulin resistance; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; PPAR, peroxisome proliferator–activated receptor; VLDL, very low-density lipoprotein.

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discussed. In addition, we provide an update on management strategies with the focus on dietary interventions and various pharmacological approaches.

2. Pathophysiology

The underlying pathophysiology of diabetic dyslipidemia is complex and still not well understood. Hypertriglyceridemia, low HDL-cholesterol and a predominance of small dense LDL can be detected years before the clinical diagnosis of type-2 diabetes in insulin-resistant, prediabetic individuals with normal glucose concentrations [4]. Thus, hyperglycemia alone cannot fully explain the lipid changes. Insulin resistance is believed to be the main trigger for diabetic dyslipidemia.

Hypertriglyceridemia is considered the dominant lipid abnormality in insulin resistance and plays a pivotal role in determining the characteristic lipid profile of diabetic dyslipidemia. Elevated triglyceride levels are the result of increased production and decreased clearance of triglyceride-rich lipoproteins in both fasting and non-fasting states. Increased production of very low-density lipoprotein (VLDL), the main transporter of fasting triglycerides, is a prominent feature of insulin resistance [5]. Insulin is involved at all stages of VLDL production and secretion. In adipose tissues, insulin suppresses lipolysis by inhibiting the activity of hormone sensitive lipase, which catalyzes the mobilization of free fatty acids from stored triglycerides. Thus, insulin regulates the amount of circulating free fatty acids, which act as substrates and regulatory factors for VLDL assembly and secretion [6]. In the liver, insulin inhibits the transcription of microsomal triglyceride transfer protein, which mediates the transfer of triglycerides to nascent apolipoprotein B (apoB), the predominant surface protein of VLDL. The production rate of apoB is relatively constant, so that the amount of apoB released is largely determined by its rate of degradation, which depends on the amount of lipidation. Consequently, the increased hepatic availability of free fatty acids leads to decreased degradation of apoB, thus causing an overproduction of VLDL in insulin resistant states [3]. Interestingly, hypoglycemia, a common condition in diabetic patients, can induce counter-regulatory processes that lead to acute elevation of free fatty acids and blunt the effects of insulin, thus promoting the production of VLDL [7].

VLDL can be divided into large, triglyceride-rich VLDL1 and small, dense VLDL2. VLDL1 has a higher triglyceride content and exhibit abundant apolipoprotein CIII (apoCIII) and apolipoprotein E [8]. VLDL1 is a strong determinant of plasma triglyceride concentration and has been shown to relate to insulin sensitivity as measured by HOMA-IR [3]. In insulin resistant individuals, VLDL1 is secreted in excess while the secretion of VLDL2 is comparable to that in insulin-sensitive individuals [5].

In addition to the overproduction of VLDL, a decrease in its clearance rate also contributes to hypertriglyceridemia. The decreased clearance rate is associated with impaired activity of lipoprotein lipase, a decrease in hepatic uptake of VLDL and an increase in postprandial triglyceride-rich chylomicrons. Lipoprotein lipase is a key enzyme in the VLDL–intermediate-density lipoprotein–LDL delipidation cascade. Elevated free fatty acids can directly disrupt the activity of lipoprotein lipase by causing it to detach from the endothelial surface [9]. Another known inhibitor of lipoprotein lipase is apoCIII, a surface protein present on apoB-containing lipoproteins and HDL. ApoCIII also hinders the hepatic uptake of triglyceride-rich lipoproteins by interfering with the binding of apoB lipoproteins to hepatic apoB or apolipoprotein E receptors [10]. The expression of apoCIII is induced by glucose and inhibited by insulin [11]. In type-2 diabetic patients, the expression of apoCIII is increased and correlates with BMI and HOMA-IR [10]. In 2 recently published epidemiological studies, loss-of-function mutations in apoCIII gene resulted in lower triglyceride levels and reduced risk of CVD [12,13].

Postprandial hypertriglyceridemia is another feature of diabetic dyslipidemia and is caused by an overproduction of both intestinal- and liver-derived triglyceride-rich lipoproteins. In type-2 diabetes, the production rate of apoB-48 is accelerated and correlates with insulin levels [14,15]. The exact mechanisms underlying these alterations are not known, but elevated levels of free fatty acids may again play an important role [16]. It was also shown that monosaccharides can acutely enhance intestinal lipoprotein production [17]. Furthermore, changes in incretins (glucagon-like peptide-1, glucagon-like peptide-2 and gastric inhibitory polypeptide) secretion and levels observed in insulin resistance may also induce postprandial hypertriglyceridemia. Intestinal-derived chylomicrons compete for the same clearance pathway as hepatic-derived VLDL, thus elevated chylomicron levels can lead to prolonged presence of VLDL in plasma and vice versa [5]. As a result, diabetic patients have increased triglyceride levels in both fasting and non-fasting states. Existing hypertriglyceridemia can be exacerbated by uncontrolled diabetes, concomitant genetic defects in lipid metabolism, alcohol abuse and certain medications. Severe hypertriglyceridemia (>1000 mg/dl) increases the risk of acute pancreatitis and requires urgent treatment and close monitoring [18,19].

An increase in triglyceride-rich lipoproteins is commonly associated with a reduction in HDL and an increase in small dense LDL levels. Hypertriglyceridemia stimulates the enzymatic activity of cholesteryl ester transfer protein (CETP), which facilitates the transfer of triglycerides from triglyceride-rich lipoproteins to HDL and LDL in exchange for cholesteryl esters [20]. This leads to an increase in triglyceride content of HDL and LDL. Triglyceride-enriched HDL particles are subject to increased catabolism; consequently, they have a short plasma half-life. Triglyceride-enriched LDL particles undergo subsequent hydrolysis via lipoprotein lipase or hepatic lipase, thereby reducing LDL particle size (Fig. 1). In addition, the difference in metabolic fate between VLDL1 and VLDL2 may also account for the increased formation of small dense LDL. Kinetic data show that large triglyceride-rich VLDL1 particles yield small dense LDL whereas smaller and denser VLDL2 particles are metabolized to normal sized LDL [21]. Interestingly, VLDL metabolism is linked not only to HDL levels but also to cholesterol efflux capacity [22].

Conventionally low HDL levels were regarded as a consequence of insulin resistance and diabetes. However, newer data indicate that low HDL may result in or exacerbate abnormal glucose homeostasis [23]. Genetic analyses in animal and human models have shed some light on the potential role of abnormal lipid metabolism in the pathophysiology of diabetes. Several genes involved in lipid metabolism also play a role in glucose