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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

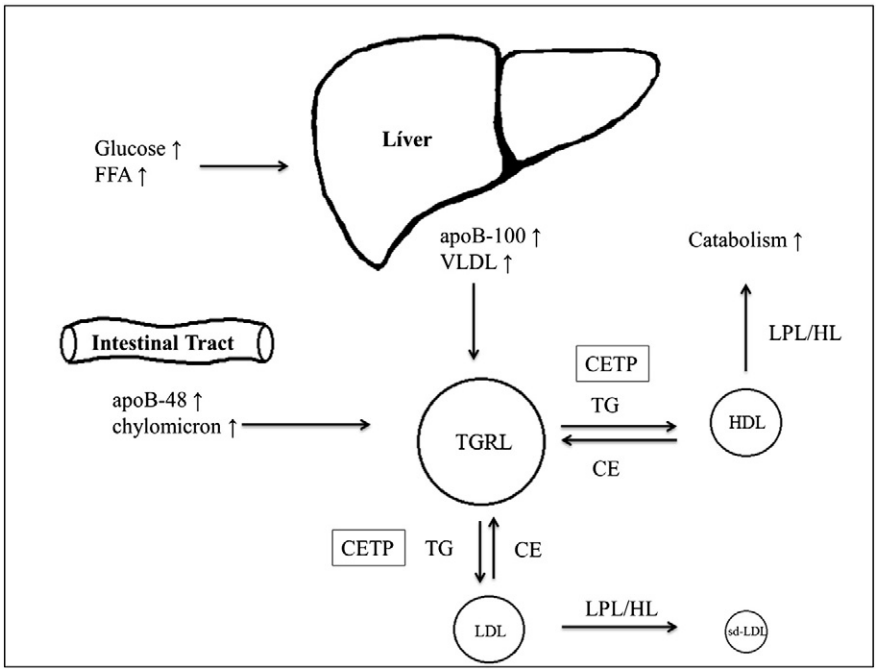

Fig. 1 – Effects of diabetes on triglyceride-rich lipoproteins, HDL and LDL. Increased availability of glucose and free fatty acids in the liver leads to decreased degradation of apoB-100 and increased secretion of VLDL. In the postprandial state, apoB-48 and chylomicrons are produced at a higher rate in the intestinal tract. Both liver-derived VLDL and intestinal-derived chylomicrons contribute to the overabundance of triglyceride-rich lipoproteins in blood. CETP facilitates the exchange of triglycerides and cholesteryl esters between triglyceride-rich lipoproteins and LDL as well as HDL. Subsequently, triglyceride-rich LDL and HDL are hydrolyzed by lipoprotein lipase or hepatic lipase. apoB: apolipoprotein; CE: cholesteryl ester; CETP: cholesterol ester transfer protein; FFA: free fatty acids; HDL: high-density lipoprotein; HL: hepatic lipase; LDL: low-density lipoprotein; LPL: lipoprotein lipase; sd-LDL: small-dense low-density lipoprotein; TG: triglyceride; TGRL: triglyceride-rich lipoprotein.

homeostasis. A particular gene that codes for ATP-binding cassette transporter, subfamily A, member 1 (ABCA1) has generated much interest. ABCA1 is a major cellular transporter of cholesterol and phospholipids, and mediates their efflux through lipidation of nascent apolipoprotein A1 (apoA1), a major component of HDL. Consequently, ABCA1 regulates the biogenesis of HDL, which is crucial for reverse cholesterol transport, the process of moving cholesterol from peripheral tissues back to the liver for excretion. Mutations in the ABCA1 gene cause accumulation of cellular cholesterol, low levels of HDL and increased risk of CVD. In mouse models, defective ABCA1 resulted in impaired glucose tolerance and abnormal insulin secretion while insulin sensitivity remained unaffected. ABCA1 is highly expressed in pancreatic islet cells. An emerging theory postulates that impaired beta cell function, which reduces insulin secretion, may be caused by accumulation of excess cellular cholesterol, in which toxic lipid metabolites induce beta cell apoptosis. This theory still warrants further research [24].

3. The relationship between diabetic dyslipidemia and CVD

Dyslipidemia increases the risk of CVD in type-2 diabetic patients. Hypertriglyceridemia, low HDL and elevated small dense LDL concentrations are all associated with CVD, but their relative contribution to the development of atherosclerotic vascular disease is still unclear. A causal relationship between LDL and atherosclerosis is well established, but not for HDL [25]. Newer data also indicate a causal role of triglyceride-rich lipoproteins in cardiovascular events [12,13,26].

Type-2 diabetic patients may not necessarily have a higher LDL concentration when compared with non-diabetic individuals [27]. However, there is a marked increase in small dense LDL particles [28], meaning that at a given LDL-cholesterol concentration, diabetic patients have a greater number of LDL particles. Small dense LDL particles are more atherogenic than large buoyant LDL [29]; they are more prone to be removed by scavenger receptors, an early critical process of atherosclerosis. At present, LDL-cholesterol remains a strong independent predictor of CVD in diabetic patients, even when the LDL level is below the National Cholesterol Education Program target of 130 mg/dl. The Strong Heart Study observed a 12% increase in CVD risk in diabetic subjects with every 10 mg/dl increase in LDL-cholesterol [30].

The main difficulty in isolating the effect of hypertriglyceridemia on CVD lies in the fact that elevated triglyceride levels are commonly associated with concomitant changes in HDL and LDL. Although population-based cohort studies have demonstrated contradictory results after adjusting for potential confounders [31], new data are in accordance with triglyceride-rich lipoproteins playing a causal role in cardiovascular events

[26]. Triglycerides are not directly involved in the development of atherosclerotic lesions because free fatty acids released from triglycerides act either as an active energy source or stored energy reserve. However, triglycerides are transported in apoB-containing lipoproteins, which may induce atherosclerosis similar to LDL. Moreover, non-fasting triglyceride is a surrogate marker for non-fasting remnant cholesterol [31]. Using data from three large Danish studies with a total of 73,513 subjects, Varbo et al. investigated the causal relationship between elevated remnant cholesterol levels and risk for coronary heart disease. The study showed that each 1 mmol/l increase in non-fasting remnant cholesterol was associated with a 2.8-fold causal risk for ischemic heart disease, independent of HDL reduction [32].

The exact role of HDL in CVD has been a long-standing conundrum. HDL has long been regarded as the "good" lipoprotein because epidemiological and clinical studies have identified an inverse association between HDL concentration and CVD [33,34]. The most important antiatherogenic function of HDL is reverse cholesterol transport [35]. HDL also exhibits other potential cardioprotective functions such as anti-oxidative, anti-inflammatory and endothelium-dependent vasodilatory effects [36]. However, some genetic variations and mutations that modulate HDL levels do not seem to affect the risk of CVD [37,38]. Furthermore, increasing HDL by pharmacological means has failed to achieve consistent and significant reduction in cardiovascular events [39]. The apparent paradox suggests that HDL concentrations per se cannot fully explain the cardioprotective effects observed in epidemiological studies. It has been postulated that HDL concentration may simply be a surrogate marker of HDL functionality and/or the concentration of triglyceride-rich apoB containing lipoproteins. The function of HDL is not well understood, in part due to its structural complexity [36]. In type-2 diabetes, there is a reduction in HDL-cholesterol concentration, which indicates an increased risk of CVD, because HDL-cholesterol is a sensitive marker for an elevated concentration of atherogenic triglyceride-rich lipoproteins. In addition, HDL function is severely impaired, further increasing the risk of CVD [40].

4. Treatment targets

Although hypertriglyceridemia plays a central role in the pathophysiology of diabetic dyslipidemia, lowering LDL remains the primary treatment target. The first step in determining treatment goals for diabetic patients is a comprehensive assessment of their cardiovascular risk. The American Diabetes Association (ADA) and European Society of Cardiology (ESC)/European Association for the Study of Diabetes (EASD) recommend reducing LDL < 100 mg/dl (2.6 mmol/l) for diabetic patients without additional cardiovascular risk. High-risk diabetic patients with additional cardiovascular risk factors should achieve a target of LDL < 70 mg/dl (1.8 mmol/l). If this cannot be achieved, lowering LDL 30%–40% (ADA) or ≥ 50% (ESC/EASD) from baseline value is an alternative goal [41,42]. The recently published American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend that any type-1 or type-2 diabetic patient between the age of 40 and 75 years and with LDL-cholesterol above 70 mg/dl (1.8 mmol/l) should receive either moderate intensity (e.g. 20 mg atorvastatin/d) or high intensity (e.g. 40 mg atorvastatin/d) statin therapy depending on the overall risk. For patients outside these boundaries (younger, older, lower baseline LDL-cholesterol) treatment should be individualized [43].

Due to the predominance of small dense LDL, diabetic individuals may have an increased number of LDL particles while LDL concentration remains normal or slightly elevated. LDL concentration does not reflect the number of LDL particles because the amount of cholesterol each particle carries varies. Since each LDL lipoprotein particle, as well as VLDL, intermediate-density lipoprotein and lipoprotein (a), contains one apoB, the concentration of apoB can be used as a surrogate marker for the total number of atherogenic lipoprotein particles [44]. ApoB and non-HDL-cholesterol concentration, which also encompasses all atherogenic lipoproteins, have been shown to be superior to LDL in predicting CVD risk in diabetic patients [45]. A practical advantage of evaluating non-HDL-cholesterol is its cost-effectiveness, since it can be directly calculated from total cholesterol minus HDL-cholesterol.

Both apoB and non-HDL-cholesterol are currently regarded as secondary treatment targets due to a lack of evidence showing that targeting apoB and non-HDL-cholesterol is superior to targeting LDL in terms of improving cardiovascular outcomes. ADA recommends a treatment target of non-HDL-cholesterol < 100 mg/dl (2.6 mmol/l) and < 130 mg/dl (3.4 mmol/l) for diabetic patients with and without an additional CVD risk factor, respectively. If apoB is used, treatment targets of < 80 mg/dl and < 90 mg/dl are desirable for those with and without an additional CVD risk factor, respectively [46]. Similarly, triglyceride and HDL-cholesterol are also secondary treatment targets. The recommended treatment goals are triglycerides < 150 mg/dl (1.7 mmol/l) and HDL >40 mg/dl (1.0 mmol/l) in men and >50 mg/dl (1.3 mmol/l) in women [41].

5. Management of diabetic dyslipidemia

Managing diabetic dyslipidemia requires a multifaceted approach. Dietary modification and pharmacotherapy are integral components of management as outlined before [47,48]. Because obesity and insulin resistance are closely linked, weight loss is an important treatment goal. Moderate weight loss (5% of body weight) is associated with improvements in insulin sensitivity, glycemic control and lipid profile [49]. Weight reduction raises HDL and decreases triglyceride levels [50]. However, the observed improvements in metabolic parameters through weight loss may not translate directly into an improvement in cardiovascular outcomes. The Look AHEAD (Action For Health in Diabetes) trial showed that long-term weight loss achieved through intensive lifestyle intervention did not decrease the rate of cardiovascular events despite an improvement in all cardiovascular risk factors, except for LDL [51]. Lifestyle intervention alone is often insufficient to achieve the strict lipid goals. In such cases, pharmacotherapy should be initiated concomitantly.

6. Diet

Diet is a key aspect in managing metabolic derangements in diabetic patients. There is a lack of consensus on the optimal macronutrient ratio that is expected to benefit all diabetic patients. Instead of recommending a specific macronutrient distribution, ADA places emphasis on individualized nutrition therapy, which takes into account a patient's current eating pattern, preferences and metabolic goals. The recently published nutrition guidelines from ADA do not provide an ideal amount of carbohydrate, protein and fat intake but make specific suggestions on nutrient sources: carbohydrate should come from vegetables, fruits, whole grain, legumes and dairy products rather than sources that contain added fat, sugar and sodium; leaner protein sources and meat alternatives are preferred; dietary fat should be mainly composed of monounsaturated and polyunsaturated fats instead of saturated and trans fat. For individuals who drink alcohol, moderate consumption (≤1 drink/day for woman and ≤2 drinks/day for men) is advised [52].

Tree nuts, a rich source of polyunsaturated fatty acids, have been shown to reduce cardiovascular events [53,54], potentially through the reduction of apoB and non-HDL-cholesterol [55]. In a pooled analysis of 25 feeding trials, nut consumption reduced triglycerides among subjects with hypertriglyceridemia (>150 mg/dl) and LDL-cholesterol in a dose-dependent manner. The observed improvement in plasma cholesterol was greatest in participants with high baseline LDL or low BMI as well as in those following a Western diet (compared to a Mediterranean or low fat diet) [56]. In addition to the cholesterol-lowering effects, nuts as a replacement for carbohydrates exhibit favorable effect on HbA1c in diabetic patients [57]. Nuts belong to the broad food category of seeds, which also include whole grains, legumes, cocoa products and coffee. Seeds are a rich source of macro- and micronutrients. Regular consumption of seeds is associated with reduced risk of CVD and type-2 diabetes [58].

Another important component of plant-based foods that has favorable effects on glycemic control and lipid metabolism is dietary fiber [59]. However, the cholesterol-lowering effect of dietary fiber is rather small at practical levels of consumption, exerting only a minimal effect on reducing CVD risk. It is difficult to isolate the effect of dietary fiber, as it may be confounded by changes in dietary pattern such as replacing saturated fatty acids with unsaturated fatty acids [60].

Many studies have tried to identify the ideal dietary pattern for diabetic patients. Among the most studied patterns are low-carbohydrate, low-fat and Mediterranean diets. A recent meta-analysis assessing different dietary patterns in the management of type-2 diabetes showed that low-carbohydrate, low-glycemic index, Mediterranean and high-protein diets all improved glycemic control compared with their respective control diets, with the largest effect observed in Mediterranean diet. Low-carbohydrate and Mediterranean diets produced greater weight loss. In addition, low-carbohydrate, low-glycemic index and Mediterranean diets significantly increased HDL by 10%, 5% and 4%, respectively; all three diets did not significantly change LDL and only Mediterranean diet significantly lowered triglycerides. The 20 studies included used various control diets, and there is a lack of direct comparison between the above-mentioned diets [61]. One study conducted a direct comparison between a low-fat diet with calorie restriction, a Mediterranean diet with calorie restriction and a low-carbohydrate diet without calorie restriction for their effects on weight loss. Subjects in all 3 diet groups lost weight, but those in the Mediterranean and low-carbohydrate diet group achieved greater weight reduction. The low-carbohydrate diet was superior in improving lipid profile (raising HDL, lowering triglyceride and ratio of total to HDL-cholesterol) when compared with the low-fat diet. Among subjects with diabetes, those in the Mediterranean diet group showed improved fasting plasma glucose level. In addition, a decrease in HOMA-IR was greatest in the Mediterranean diet group [62]. Beyond the beneficial effects on lipid and glucose metabolism, Mediterranean diet also improves other components of the metabolic syndrome namely waist circumference and blood pressure [63].

Although some dietary patterns may seem to be more favorable than other in some aspects, there is no single "best" dietary pattern for all diabetic patients in the management of dyslipidemia.

7. Drug therapy

Normalizing blood glucose levels is a top priority for all diabetic individuals with poor glycemic control because hyperglycemia can exacerbate lipid abnormalities, particularly hypertriglyceridemia. Currently available oral anti-diabetic agents have varying effects on plasma lipids. Incretin-based therapies are novel agents that have been shown to improve both fasting and postprandial lipid profile [64]. Glitazones, which activate peroxisome proliferator-activated receptor-γ (PPAR-γ), are unique in improving insulin resistance, and they may be superior to sulfonylureas in improving plasma lipids [65]. PPAR-α/PPAR-γ dual activators, which are pharmacologically more related to fibrates, have shown beneficial effects on glucose and lipid metabolism; however serious side effects have prevented their clinical use [66].

While lifestyle modification and glucose control may help to prevent microvascular complications of diabetes, they have little effect on cardiovascular events. Statin-based lipid lowering therapy, on the other hand, has been shown to reduce cardiovascular morbidity and mortality in a wide range of diabetic patients [67]. Diabetic dyslipidemia should therefore be treated with statins. However, significant residual risk remains, making many patients candidates for potential combination therapy (Table 1, Fig. 2).

8. Statins

Statins remain the first-line therapy in the management of dyslipidemia. ADA recommends that statins should be used, regardless of baseline lipid levels, in diabetic patients with CVD or who are over the age of 40 and have one or more CVD risk factor including family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria. Statin therapy is also recommended for diabetic patients under the age of 40 with

Table 1 – Lipid lowering combination therapy in diabetic dyslipidemia.

Statin +	Lipid effect	Outcome information
Ezetimibe	LDL↓↓	No meaningful outcome trial in diabetic patients available;
Fibrates	TG ↓↓, HDL ↑↑, LDL (↓)	Negative outcome trials in diabetic patients [68]; limitation: subgroup with elevated triglycerides and low HDL-cholesterol may benefit;
Omega-3 fatty acids	TG ↓↓, HDL ↑,	Negative outcome trial in patients with impaired fasting glucose, impaired glucose tolerance or early type 2 diabetes [69]; limitation: low dose of omega-3 fatty acids was used;
Bile acid sequestrant	LDL ↓↓, TG ↑,	No outcome trial with concomitant statin therapy; older trials suggest benefit in patients not on statins [70,71];
Niacin	TG↓↓, HDL ↑↑, LDL ↓↓, Lp(a) ↓↓	Negative outcome trials in diabetic and non-diabetic patients [72,73]; limitation: very low baseline levels (on statin therapy);

LDL: low density lipoprotein; TG: triglycerides; HDL: high density lipoprotein; Lp(a): lipoprotein(a); ↓↓/↑↑: indicates >15% change; ↓/↑: indicates <15% change; (↓): indicates variable effect.

multiple CVD risk factors or LDL > 100 mg/dl (82.6 mmol/l) despite lifestyle intervention [41]. Similarly, the recently published ACC/AHA guidelines recommend that any type-1 or type-2 diabetic patient between the age of 40 and 75 years and LDL-cholesterol above 70 mg/dl (1.8 mmol/l) should receive statin therapy [43]. Statins are most effective at lowering LDL and, to a lesser extent, also lower triglycerides and raise HDL. In addition, statins have anti-inflammatory and anti-thrombotic properties and the ability to stabilize atherosclerotic plaques [74].

The CARDS (Collaborative Atorvastatin Diabetes Study) was the first large primary prevention study to evaluate specifically the effect of statin on cardiovascular outcomes in type-2 diabetic individuals without pre-existing CVD. Results showed that a daily dose of 10 mg of atorvastatin was associated with a 37% reduction in major CVD events and particularly with a 48% decrease in the incidence of stroke [75]. However, many diabetic patients remain at high risk for cardiovascular events despite achieving their LDL goals. This residual cardiovascular risk in individuals receiving an adequate statin therapy has been attributed to elevated triglycerides and low HDL [76].

Although statins clearly improve CVD outcomes, they are associated with increased risk of developing diabetes [77]. The underlying mechanisms are still unclear. Activation of certain pro-inflammatory proteins by statins may play a role in inducing insulin resistance but changes in cholesterol metabolism of beta-cell may also be important [78]. However, the beneficial effects of statins still outweigh their potential diabetogenic effects.

9. Cholesterol absorption inhibitors

Cholesterol absorption inhibitors are a class of hypocholesterolemic drug that inhibits intestinal cholesterol absorption. Ezetimibe is effective at lowering LDL-cholesterol, especially when combined with statin. In one study, the combination of ezetimibe/simvastatin (10 mg/20 mg) was more effective at reducing LDL-cholesterol, non-HDL-cholesterol and total cholesterol/HDL-cholesterol ratio in subjects with and without diabetes than doubling the dose of simvastatin (40 mg). Furthermore, the proportion of subjects achieving the goal of LDL-cholesterol < 100 mg/dl (2.6 mmol/l) was higher in the ezetimibe/simvastatin group [79]. Ezetimibe reduces the cholesterol content of both fasting and postprandial triglyceride-rich lipoproteins, thereby lowering the concentrations of atherogenic remnant particles [80]. Although the hypocholesterolemic effect of cholesterol absorption inhibitors is well-established, convincing data on cardiovascular outcomes are still lacking.

10. Fibrates

Fibrates are the most potent drugs for lowering triglycerides. They also lower LDL and raise HDL. In a meta-analysis of 6 randomized controlled trials with a total of 15,000 subjects with hypertriglyceridemia and low HDL, fibrate treatment was associated with a 16%–29% risk reduction in vascular events [81]. Considering the persistent hypertriglyceridemia in many statin-treated diabetic patients, the addition of a fibrate to statin therapy may appear to be a reasonable therapeutic approach. However, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Lipid trial showed that fenofibrate did not provide additional reduction in cardiovascular events when combined with simvastatin. But in a subgroup analysis of subjects with triglyceride level in the highest tertile (≥204 mg/dl) and HDL-cholesterol in the lowest tertile (≤34 mg/dL), 31% reduction in cardiovascular events in the combination-therapy group (interaction $P = 0.057$) was observed [68]. In addition, a subgroup of 139 subjects in the ACCORD Lipid trial showed that the combination of fenofibrate and statin significantly reduced postprandial triglycerides when compared with statin plus placebo [82].

Fibrates can be used to treat isolated hypertriglyceridemia. The combination with statin should be considered on an individual basis. Subjects at high risk with high triglyceride levels and low HDL levels may benefit from the combination therapy. The statin–fibrate combination should be applied with caution due to the increased risk for myopathy and rhabdomyolysis, especially when combining statin with gemfibrozil. The combination of statin with fenofibrate or bezafibrate is better tolerated and should be preferred [83].

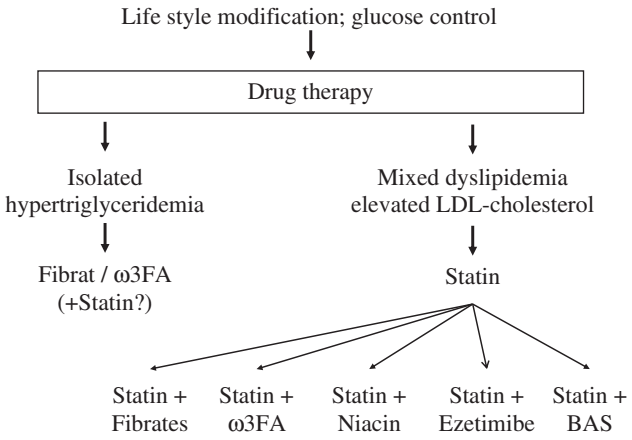

Fig. 2 – Treatment algorithm for diabetic dyslipidemia. Lifestyle modification and glucose control should be used to improve lipid levels. However, most patients will require statin therapy. In patients with isolated hypertriglyceridemia (elevated triglycerides and LDL-cholesterol < 70 mg/dl), fibrates or omega-3 fatty acids may be used; the role of statins is unclear in such patients. Combination therapies may be considered in patients at very high risk; however, they are not proven by outcome studies. The combination of statins with ezetimibe (cholesterol absorption inhibitor) can significantly decrease LDL-cholesterol. The combination of statins with fibrates or omega-3 fatty acids decreases triglycerides, while the combination of statins with bile acid resins decreases LDL-cholesterol and may increase triglycerides. LDL: low-density lipoprotein; ω3FA: omega-3 fatty acids; BAS: bile acid sequestrant.

11. Niacin

Niacin is currently the most potent drug in raising HDL-cholesterol. In type-2 diabetic subjects, this is mediated through a decreased catabolism of apoA1 containing particles [84]. Niacin also has moderate effect in lowering LDL-cholesterol, triglycerides and lipoprotein(a). However, the combination of niacin and statin has not been shown to provide additional cardiovascular benefits when compared with statin monotherapy in 2 outcome studies [72,85]. However, both outcome trials, the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes) [72] and the HPS-2 THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) [85], have been under scrutiny due to their potential methodological flaws which could have contributed to the failure of niacin to improve CVD endpoints. Both studies included a high percentage of subjects who had already reached strict lipid goals and would normally not require additional lipid therapy. In the AIM-HIGH study, each placebo tablet contained 50 mg of immediate-release niacin to cause mild flushing, thus ensuring that the treatment remained blinded. This has caused some to argue that the study was not a direct comparison between niacin and placebo but rather a study of high-dose vs. low-dose niacin. The use of niacin/laropiprant combination in the HPS-2 THRIVE study also raises the question whether the negative-side effects could in fact be off-target effects of laropiprant, a prostaglandin D2 inhibitor, and not niacin. In light of these uncertainties, the final verdict on the effectiveness of niacin remains inconclusive.

12. Bile acid sequestrants

Bile acid sequestrants (BAS) bind to bile acids in the intestinal lumen, thereby interrupting the enterohepatic circulation of bile acids. As a result, the liver increases the production of bile acids, which leads to a decrease in cholesterol pool. BAS lower plasma total and LDL-cholesterol while raising HDL-cholesterol and apoA1. The cholesterol-lowering effect of BAS may be accompanied by an increase in triglycerides [86]. Diabetic patients may also benefit from the favorable effects of BAS on glucose homeostasis. Colesevelam monotherapy improves HbA1c in patients with inadequately controlled diabetes [87]. Studies suggest that the glucose-lowering mechanisms of colesevelam may differ from that of other antidiabetic agents, making it a potential drug for combination therapies in managing type-2 diabetes [88].

Currently BAS are considered a second-line treatment option in individuals with statin intolerance. Furthermore, BAS can be used in combination therapy. Further studies are needed to assess the effect of BAS on cardiovascular outcomes in diabetic patients.

13. Omega-3-fatty acids

Omega-3 fatty acids lower triglycerides but have little effect on LDL and HDL. In addition to hypotriglyceridemic effects, omega-3 fatty acids may attenuate inflammation, improve endothelial function and reduce thrombus formation [89]. Despite having multiple cardioprotective effects, omega-3 fatty acids have not been shown to improve cardiovascular outcomes in diabetic patients. In the ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial, 12,536 subjects who were at high risk for cardiovascular events and had impaired fasting glucose, impaired glucose tolerance or diabetes were randomized to receive a daily 1 g supplementation of omega-3 fatty acids or placebo. In the median follow-up of 6.2 years, cardiovascular mortality did not decrease significantly in subjects receiving omega-3 fatty acids when compared with placebo [69].

14. Potential therapeutic compounds

New hypolipidemic therapies are being developed to improve the management of dyslipidemia (Table 2). Among new therapeutic compounds, apoB antisense oligonucleotide (mipomersen) and microsomal triglyceride transfer protein inhibitor (lomitapide) are approved by the U.S. Food and Drug Administration to treat homozygous familial hypercholesterolemia [98], while others such as CETP inhibitors, apoCIII antisense oligonucleotides, apoCIII antibodies and proprotein

Table 2 – Emerging therapeutic strategies potentially useful in diabetic dyslipidemia.

Therapeutic Agents	Dominant Lipid Effect	Mechanism
CETP inhibitors (anacetrapib, evacetrapib) [90,91]	HDL↑ LDL↓	Inhibit the transfer of cholesteryl esters and triglycerides between triglyceride-rich lipoproteins and HDL as well as LDL;
ApoB antisense oligonucleotide (mipomersen) [92]	LDL↓, Lp(a) ↓	Bind to apo B-100 mRNA, thereby blocking the translation of the gene product;
MTP inhibitor (lomitapide) [93]	LDL↓	Inhibit the lipidation of apoB in liver and enterocytes;
PCSK 9 antibodies [94–96]	LDL↓, Lp(a) ↓	Inhibit the lysosomal degradation of LDL receptors, consequently increasing their cell surface expression;
ApoCIII antisense oligonucleotides [97]	Triglyceride ↓	Bind to apoCIII mRNA, thereby blocking the translation of the gene product and consequently decrease the secretion of VLDL and chylomicrons;

ApoB: apolipoprotein B; ApoCIII: apolipoprotein C-III; CETP: cholesteryl ester transfer protein; MTP: microsomal triglyceride transfer protein; PCSK 9: proprotein convertase subtilisin/kexin type 9; VLDL: very-low density lipoprotein.

convertase subtilisin/kexin type 9 (PCSK9) antibodies are currently under clinical evaluation.

Of these new drugs, PCSK9 antibodies are probably the most interesting compounds as they can decrease LDL-cholesterol in addition to statins by up to 60% [94]. PCSK9 is a protein primarily expressed in liver, intestine and kidney. It binds to LDL receptors and promotes their degradation, consequently reducing the removal of LDL from plasma. While gain-of-function mutations of PCSK9 cause hypercholesterolemia, loss-of-function mutations are associated with hypocholesterolemia and reduced risk of CVD [99,100].

The aforementioned compounds are prospective therapeutic options for patients with severe hypercholesterolemia or statin-intolerance. Their role in the management of diabetic dyslipidemia cannot be determined at this point.

15. Conclusions

Diabetic dyslipidemia is a widespread condition, in which insulin resistance is considered the driving force behind the characteristic lipid abnormalities. All three components, namely hypertriglyceridemia, low HDL-cholesterol and high small dense LDL levels, are metabolically linked, with hypertriglyceridemia being the dominant feature. Effectively managing diabetic dyslipidemia is significant in reducing the risk of CVD. Lifestyle and pharmacological interventions are the most important treatment strategies. Consequent treatment with statins is so far the most effective approach to decrease cardiovascular risk in diabetic patients. However, significant residual risk in statin-treated patients and statin intolerance in some patients still remain an unsolved problem. The role of statin in raising the risk for newly onset diabetes also warrants further research. In the quest for new therapeutic strategies, it is crucial to further promote the understanding of the underlying pathophysiology of lipid abnormalities in diabetic patients and to expand the existing knowledge on already established lipid-lowering drugs to clearly identify their role in the management of diabetic dyslipidemia.

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