

Lipid Disorders in Diabetes Mellitus and Current Management

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Abstract: Lipid disorders are common in diabetes mellitus (DM), and play crucial roles in the development of diabetic cardiovascular complications. Diabetic dyslipidemia is characterized by hypertriglyceridemia, increased levels of very low density lipoproteins (VLDL), small dense low density lipoprotein (LDL), and decreased levels of high density lipoprotein (HDL)-cholesterol. The activity of lipoprotein lipase is reduced in diabetic patients, which attenuates the lipolysis of triglyceride-rich lipoproteins and the uptake of free fatty acids. The increased uptake of triglycerides in liver promotes the production of VLDL. Hypertriglyceridemia promotes the exchange of cholesteryl ester from HDL to VLDL or LDL for triglycerides. Obesity or nephropathy deteriorates the dyslipidemia in DM patients. The initial management of lipid disorders in diabetic patients without cardiovascular disease is lifestyle intervention and glucose control. The abnormalities in the metabolism of LDL or HDL in diabetic patients often require pharmacological intervention. Target of LDL-cholesterol (LDL-c) is more restrict in diabetic patients than in non-diabetic subjects. Treatment with HMG-CoA reductase inhibitors (statins) effectively reduces LDL-c and cardiac events, and that was associated with moderately increases in HDL-c. The combination of ezetimibe with a statin helps to achieve LDL-c target in patients with unsatisfactory cholesterol lowering by statin alone. Fibrates (PPAR- α agonists) or PPAR- γ agonists reduce the levels of triglycerides and moderately elevate HDL-c. PPAR- γ agonists also improve insulin sensitivity. Cholesteryl ester transfer protein inhibitors may dramatically increase HDL-c. Lipid management has been considered as an effective approach to reduce cardiovascular risk in diabetes.

Keywords: Dyslipidemia, Diabetes, Cardiovascular complications, Lipid and lipoprotein metabolism, Pharmacological management of lipid disorders.

INTRODUCTION

Incidences of diabetes mellitus (DM) have been rapidly increased in most of industrialized and many developing countries during last thirty years, and the trend of the increase is continuing [1]. Due to the wide application of hypoglycemic agents, diabetic ketoacidosis is rarely seen in current clinical practice. Cardiovascular complications become the predominant cause of death in diabetic patients [2]. Results from prospective studies indicated that the risk for atherosclerotic coronary artery disease (CAD) is increased by 2-4-fold in type 1 or type 2 DM [3, 4]. Diabetes is the major cause of blind (diabetic retinopathy), chronic renal failure (diabetic nephropathy) and amputation (diabetic neuropathy) in North America [5]. Mechanism for the increased susceptibility of diabetic patients to cardiovascular diseases remains poorly understood. Dyslipidemia is a common feature of diabetes and CAD. A number of large randomized clinical trials demonstrated that lipid lowering successfully reduced cardiovascular events and death in patients with diabetes (for a recent review, see reference 6). The present review summarizes up-to-date knowledge on the pathophysiology and the management of diabetic lipid disorders.

DYSLIPIDEMIA IN DIABETIC PATIENTS

Type 1 or Insulin-Dependent DM

The levels of serum triglycerides are greatly elevated in type 1 DM patients with poor glucose control, which is due

to the accumulation of chylomicrons and very low density lipoproteins (VLDL) in blood circulation. Elevated cholesteryl ester in VLDL was found in diabetic patients [7-9]. The levels of low density lipoproteins (LDL)-cholesterol in type 1 DM patients are often normal, but the levels of triglyceride-rich LDL, or small dense LDL, are frequently increased. The levels of high density lipoprotein (HDL)-cholesterol or the ratio between cholesterol and triglyceride in HDL are often reduced in type 1 DM. In type 1 DM patients without nephropathy, the levels of triglycerides, VLDL, LDL and HDL-cholesterol are usually corrected to normal ranges through glucose control. Compositional changes in lipoproteins are often not normalized by hypoglycemic treatment [10, 11].

Type 2 or Non-Insulin-Dependent DM

The elevations of triglycerides or chylomicronemia in type 2 DM with suboptimal glucose control are not evident as that in type 1 DM. The levels of total and LDL-cholesterol in type 2 DM patients are often increased or subnormal. Elevated levels of small, dense LDL have frequently been detected in type 2 DM patients [12]. A decreased level of HDL-cholesterol is often detected in patients with type 2 DM. That is associated with elevated levels of apolipoprotein B (apoB) and decreased levels of apoA1. Hypoglycemic therapy alone usually does not normalize the dyslipoproteinemia in type 2 DM patients [13].

Gestational DM (GDM)

GDM is carbohydrate intolerance first recognized during pregnancy. Increased incidence of type 2 DM have been found in mothers with GDM and their offspring [14]. During

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normal pregnancy, the levels of cholesterol and triglycerides are reduced at approximately 7 weeks of gestation, and then increase progressively till term. The levels of lipids usually return to normal ranges after delivery [15]. Increased triglycerides and decreased HDL-cholesterol are often detected in GDM [16]. Insulin sensitivity is reduced in GDM patients [17].

Postprandial Hyperlipidemia

Under normal conditions, the level of triglyceride-rich lipoproteins (chylomicrons and VLDL) and is temporarily increased after meal and rapidly normalized through increased activities of insulin and lipoprotein lipase (LPL). The activity of LPL is up-regulated by insulin. Prolonged postprandial hypertriglyceridemia is frequently detected in type 1 or type 2 DM patients, possibly due to attenuated LPL activity subsequent to insufficient insulin secretion. Postprandial triglycerides associated with increased apoB-48 (associated with chylomicron) and retinyl palmitate (rich in remnant chylomicron) are detected in CAD patients [18-20]. Increasing lines of evidence suggest that the disorders of triglyceride-rich lipoproteins may be atherogenic [21].

Insulin Resistance

Insulin is the key hormone modulating the metabolism of glucose and lipids (particularly triglycerides and fatty acids). Insulin resistance is defined as diminished tissue responses

to insulin at one or more sites in the complex pathways of the hormone action, which is associated with hyperinsulinemia. The biological actions of insulin are exerted through a transmembrane insulin receptor, which leads to the recruitment of insulin receptor substrate (IRS). Depending on targeted tissues and metabolic processes, the activation of IRS is often coupled with phosphatidylinositol-3 kinase (PI3K)/Akt (protein kinase B) pathway or Shc (Src homology collagen)/mitogen activating protein (MAP) kinase pathway [22] (Fig. 1). Insulin resistance in skeletal muscle in terms of glucose transport and utilization may be induced by a defect in the pathway, including reduced insulin receptor expression, impaired IRS phosphorylation, or attenuated PI3K/Akt activity [23]. Insulin also mediates the esterification of free fatty acids (FFA) in adipose tissue and reduces the levels of FFA in blood circulation after meals. In patients with obesity, the levels of postprandial FFA are elevated even with the presence of hyperinsulinemia [24]. Insulin resistance has been considered as the major underline mechanism for the development of type 2 DM.

Metabolic Syndrome

Metabolic syndrome, a cluster of manifestations of insulin resistance, has been considered as an indicator for increased risk of CAD and type 2 DM. The definition of metabolic syndrome has not been unified. The most frequently used criteria for metabolic syndrome are from

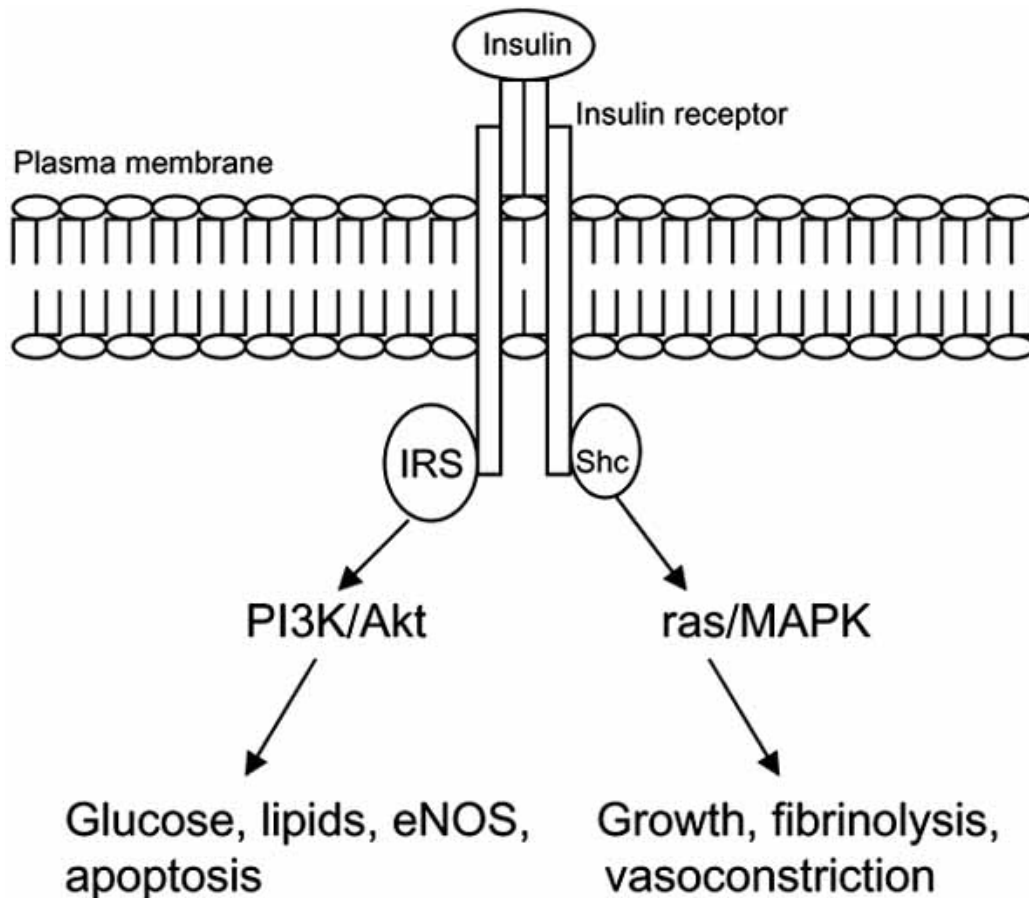


Fig. (1). Scheme for insulin signal transduction and cellular effects. IRS: insulin receptor substrate; PI3K: phosphatidylinositol-3 kinase; Akt: protein kinase B; Shc: Src homology collagen; MAPK: mitogen activating protein kinase; eNOS: endothelial nitric oxide synthetase.

World Health Organization (WHO) [25] and National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [26]. Hypertriglycemia or low HDL-cholesterol has been considered as one of the five risk factors in the WHO criteria. In the NCEP-ATP III criteria, hypertriglycemia and low HDL-cholesterolemia are considered as two out of five independent risk factors (Table 1). The NCEP-ATP III criteria do not include insulin sensitivity. The WHO criteria require assessment of insulin sensitivity using fasting insulin or homeostasis model (HOMA-IR). However, the measurement of insulin is not always accessible to many institutes and the methods for insulin measurement vary between institutes. The inclusion of type 2 DM in the WHO criteria is controversial, since type 2 DM is expected to be an outcome of the metabolic syndrome. The criteria of hypertension is more restrict in the WHO criteria (>140/90 mmHg) than in the NCEP-ATP III criteria (>130/85 mmHg). Obesity is estimated using body mass index (BMI) or waist/hip ratio in the WHO criteria. The NCEP-ATP III criteria recommend to using waist circumference. Waist circumferences are expected to vary between ethnic groups. Lower upper limits on waist circumference (male >94 cm and female >80 cm) have been adapted in Europe [27]. The age-adjusted prevalence of the NCEP-ATP III metabolic syndrome was 26.6% in Mexico, but it was significantly lower in the same population using the WHO criteria (13.6%) [28]. In spite of the limitations of the existing criteria, the concept of metabolic syndrome is widely accepted since it helps to identify individuals with increased risk for type 2 DM or cardiovascular disease.

Regulation of Lipid Metabolism in Diabetes

LPL

LPL is a serine hydrolase. It is synthesized in multiple types of cells, including adipocytes, cardiomyocytes and smooth muscle cells (SMC). LPL binds to proteoglycan on vascular endothelial surface after it enters blood circulation. LPL becomes active after it is released from endothelial surface by heparin. LPL mediates the hydrolysis of triglycerides in chylomicrons or VLDL. Heparin enhances the activity of LPL. The prime products of LPL are monoacylglycerol and FFA. LPL also promotes the uptake of FFA by adipocytes. Insulin promotes the activity of LPL.

Attenuated LPL activity contributes to dyslipidemia in diabetes [29, 30].

Hormone Sensitive Lipase (HSL)

HSL is mainly expressed in adipocytes. The phosphorylations of HSL at Ser659 and Ser660 positions are required for the activation of HSL [31]. Under metabolic stress, ex. fasting or exertion, HSL is activated. HSL facilitates the hydrolysis of esters on the 1 and 3 positions of triglycerides in adipocytes. The hydrolysis of the ester on the 2 position of triglycerides is mediated by monoacylglycerol lipase. The activity of HSL is stimulated by catecholamine through β -adrenergic receptor. Insulin suppresses HSL-mediated lipolysis during fasting. Resistance to the effect of insulin on HSL-induced lipolysis has been detected in obese or non-obese individuals with insulin resistance or type 2 DM [32, 33].

Cholesteryl Ester Transfer Protein (CETP)

CETP is a lipid transfer protein synthesized in hepatocytes. It forms complex with lipoproteins in blood circulation. CETP mediates the transfer of triglycerides from VLDL, IDL or LDL to HDL in an exchange for cholesteryl esters. The activity of CETP is mainly regulated by substrates, particularly triglyceride-rich lipoproteins [34]. The activity of CETP is increased in patients with type 1 or type 2 DM [35, 36], which may be partially responsible to low HDL-cholesterol and high triglyceride-rich lipoproteins in diabetic patients.

Production of VLDL

The lipids and apoB-100 are assembled into VLDL in liver with the assistance of microsomal triacylglycerol transfer protein [37]. The increased uptake of remnant chylomicrons and FFA in liver promotes the synthesis of triglycerides and apoB-100. Insulin acutely inhibits VLDL production in fasting humans [38]. With the presence of insulin resistance, obesity and type 2 DM, the acute inhibitory effect of insulin on VLDL production is suppressed [39, 40]. Chronic hyperinsulinemia or carbohydrate ingestion enhances the transcription and certain lipogenic enzymes (sterol-regulatory element binding protein 1, fatty acid

Table 1. Comparison of WHO and NCEP Criteria for Metabolic Syndrome

	WHO *	NCEP-ATP III **
Blood pressure (mmHg)	>140/90	>130/85
Hyperglycemia	IGT or type 2 DM	>110 mg/dL (changed to >100 mg/dL)
Lipids (mg/dL)	TG \geq 150 or HDL-c <35-40	TG \geq 150 HDL-c <40-50
Obesity	BMI >30 kg/M ² or waist/hip ratio >0.85 (women), >0.9 (men)	Waist circumference >102 cm (men) >88 cm (women)
Insulin resistance	Fasting insulin >75 th percentile or HOMA-IR >75 th percentile	
Other	Microalbuminuria	

WHO: World Health Organization; NCEP-ATP III: National Cholesterol Education Program Adult Treatment Program III; IGT: impaired glucose tolerance; DM: diabetes mellitus; TG: triglycerides; HDL-c: high density lipoprotein-cholesterol; BMI: body mass index; HOMA-IR: homeostasis model assessment for insulin resistance.

*: metabolic syndrome is indicated if \geq 2 risk factors plus type 2 DM, IGT or insulin resistance are presented.

** : metabolic syndrome is indicated if \geq 3 risk factors are presented.

synthetase and acetyl-coenzyme A carboxylase), which enhances lipid synthesis in the body [41].

Mobilization of FFA

The level of FFA in blood circulation is determined by following factors: i) the release of FFA from triglyceride-rich lipoproteins; ii) the lipolysis of triglycerides in adipose tissue; iii) the uptake of FFA by adipose tissue or liver; and iv) the oxidation of FFA in tissues, mainly in muscle, heart and liver [42]. FFA is mainly carried by albumin in circulation. Decreased albumin levels in diabetic nephropathy may aggravate dyslipidemia in diabetic patients. Elevated fasting and postprandial FFA have been found in patients with obesity or type 2 DM [43, 44]. The levels of fasting plasma FFA correlated with decreased insulin-mediated glucose disposal in the first degree relatives of type 2 DM patients [45], which suggests that abnormally increased FFA may be an early sign of glucose intolerance.

Impact of Obesity on Lipid Metabolism

In North America, approximately a half of adults and one fifth of children are obese or overweight. Obesity is a classical risk factor for type 2 DM and CAD. Central or visceral obesity is closely associated with metabolic syndrome, type 2 DM or CAD. Unhealthy eating habit and physiological inactivity have been considered as etiological factors for obesity. Obesity is a complex metabolic state, which is characterized by expanding the mass of adipose tissue with increased content of triglycerides. Elevated levels of plasma FFA and insulin resistance are crucial in the development of obesity. Insulin-mediated suppression of lipolysis by HSL is defective in obese or insulin resistance subjects [46, 47]. Lipogenesis in white adipose tissue from obese subjects or those with insulin resistance is attenuated due to decreased glucose uptake and diacylglycerol acyltransferase activity (the rate-limiting enzyme of triglyceride synthesis) [48]. Reduced lipogenesis promotes the release of fatty acids from adipose tissue, which inhibits LPL activity. The regulation of LPL activity in responding to insulin is defective in obese or insulin resistance subjects [49, 50]. Increased levels of VLDL or chylomicron promote the transfer of cholesteryl ester from HDL to VLDL and LDL, which partially explains the low levels of HDL-cholesterol in obese subjects.

Adipokines and Lipid Metabolism

Leptin

Leptin, the product of *ob* gene, was first discovered in obese and insulin resistant *ob/ob* mice. Leptin is mainly synthesized in adipose tissue, but it is also expressed in muscles, stomach and placenta [51]. The expression and secretion of leptin is regulated by hormones and nutritional signals. Insulin stimulates the expression and release of leptin [52]. Obesity, weight gain or re-feeding increases the levels of leptin. High fat diet, short term fasting or weight loss reduces the levels of leptin [53]. Leptin is a lipolytic hormone. FFA generated from leptin-induced lipolysis is towards to oxidation, thus increases energy expenditure [54, 55]. The administration of recombinant leptin reduces food intake and body weight in animals and in humans [56-58].

Hyperleptinemia is associated with insulin resistance and type 2 DM [59], which possibly is due to leptin resistance.

Adiponectin

The expression of adiponectin is only detected in adipose tissue. Insulin increases the expression of adiponectin in adipocytes [60]. Adiponectin decreases plasma glucose, postprandial FFA, and triglycerides in muscle or liver, and increases the oxidation of FFA in muscle. Daily administration of adiponectin induces weight loss in mice on high sucrose diet without affecting their food intake [61, 62]. Adiponectin is downregulated in obesity and type 2 DM [63, 64]. Decreased levels of adiponectin were detected in blood circulation of type 1 DM patients [65].

Resistin

Resistin, a relatively new member of adipokine family, is synthesized in liver. Resistin impairs glucose intolerance, reduces insulin-mediated glucose intake, and increases hepatic glucose production [66]. The antibody of resistin normalizes insulin-induced glucose uptake in adipocytes [67]. FFA stimulates the expression of resistin in adipocytes and liver, which is associated with insulin resistance in animal model [68, 69]. The levels of resistin are increased in obesity and DM [70]. The effect of insulin on resistin remains controversial [71, 72].

Tumor Necrosis Factor (TNF)- α

TNF- α , a marker of inflammation, is expressed in macrophages and adipocytes. TNF- α stimulates lipolysis and suppresses FFA uptake, adipocyte differentiation, and the expression of LPL and acetyl CoA synthetase [73, 74]. TNF- α stimulates the secretion of leptin [73], suppresses the synthesis of insulin [75] and adiponectin [76]. The knockout of TNF- α gene improves insulin sensitivity and reduces FFA levels in *ob/ob* mice [77]. The neutralization of TNF- α increases insulin-mediated glucose uptake in obese *fa/fa* mice [78]. The plasma levels of TNF- α and its expression in adipose and muscle tissues are elevated in type 2 DM [79, 80]. However, the administration of TNF- α neutralizing antibody failed to improve insulin sensitivity in obese patients with type 2 DM [81].

Interleukin (IL)-6

The expression of IL-6 has been found in monocytes, macrophages, adipocytes, fibroblasts, endothelial cells (EC) and SMC. IL-6 is increased in diabetes and atherosclerotic cardiovascular disease [82, 83]. Up to 35% of IL-6 is generated from white adipose tissue [84]. IL-6 is another important mediator of inflammation. Increased IL-6 levels are found after high fat meal [85]. IL-6 increases the production and release of hepatic glucose [86, 87]. IL-6 infusion elevates serum levels of FFA and triglycerides [88]. However, IL-6-deficiency develops mature-onset DM with impaired glucose clearance [89]. The overexpression of IL-6 in non-obese diabetic mice delays the onset of DM [90]. IL-6 administration inhibits the production of TNF- α [91] and induces the release of soluble TNF- α receptor, which may neutralize the effect of TNF- α [92].

Plasminogen Activator Inhibitor (PAI)-1

PAI-1, the physiological inhibitor for tissue and urokinase plasminogen activators, is synthesized in hepatocytes, adipocytes, vascular EC and SMC. PAI-1 inhibits the degradation of intravascular fibrin clots or extracellular matrix remodeling [93]. Elevated levels of PAI-1 are associated with insulin resistance, obesity and DM [94], and have been considered as a non-traditional risk factor for CAD [95]. The production of PAI-1 is up-regulated by thrombin, IL-1, endothoxin, transformation growth factors, glucocorticoid, fatty acids, VLDL, LDL or their modified forms [96-100]. A recent study in PAI-1 knockout mice suggests that PAI-1 plays an important role in obesity and insulin resistance. PAI-1 deficiency prevented obesity and insulin resistance induced by high fat diet in mice [101].

Hyperlipidemia in Diabetic Nephropathy

Diabetes is the single largest cause of end stage renal disease (ESRD) in North American, which requires dialysis or kidney transplantation [102]. Microalbuminuria and hypertension occur 5-15 years after the start of type 1 or type 2 DM. Progress from microalbuminuria to ESRD usually takes 5-10 years [103]. The loss of albumin from urine increases the levels of FFA in plasma. High levels of FFA stimulate the synthesis of triglycerides and the production of VLDL in liver. The increased levels of triglyceride-rich lipoproteins enhance cholesteryl ester transfer and reduce HDL-cholesterol. Diabetic nephropathy is an independent causative factor for dyslipidemia, which aggravates the lipid disorders in diabetic patients.

Glycation and Oxidative Modification of Lipoproteins

The levels of glycated proteins, including lipoproteins, are elevated in diabetic patients. Glycation increases the susceptibility of LDL to oxidation [104]. Oxidation enhances the atherogenicity of lipoproteins [105]. Increased oxidative stress or lipid peroxidation products were not only detected in diabetic patients with dyslipidemia [106], but also in normolipidemic diabetic patients [107]. The content of lipid peroxides is elevated in glycated LDL [108]. The clearance of glycated LDL from circulation through the LDL receptor is delayed [109]. Recent studies in our laboratory demonstrated that treatment with glycated LDL induced a greater release of hydrogen peroxide from cultured vascular EC than LDL [110]. LDL from diabetic patients as well as LDL glycated *in vitro* increases platelet activation [111] and the production of PAI-1 in EC [108, 112, 113]. The findings suggest that glycation enhances the atherothrombogenicity of lipoproteins, which may contribute to the accelerated development of cardiovascular complications in diabetic patients.

MANAGEMENT OF LIPID DISORDERS

Target of Lipid Lowering

It has been widely accepted that more restrict lipid lowering is required for diabetic patients than for non-diabetic subjects in order to prevent cardiovascular diseases. According to the NCEP guideline, the target level of serum LDL-cholesterol for diabetic patients without overt

cardiovascular disease is <100 mg/dL [114, 115]. Canadian Diabetes Association Guidelines 2003 recommends that the target levels of LDL-cholesterol are <2.5 mM/L (95 mg/dL) for diabetic patients without cardiovascular complications [116].

Lifestyle Intervention

Initial management for lipid disorders in all types of diabetes (type 1 DM, type 2 DM or GDM) is lifestyle intervention, including weight loss and increased physical activity. Low fat and low cholesterol diet is recommended to diabetic patients. Plant sterols may reduce the absorption of cholesterol [117]. Exercise may improve insulin sensitivity. Exercise alone without weight control does not effectively improve lipid profile in subjects with glucose intolerance or type 2 DM patients [118]. Exercise may improve the anti-inflammatory capacity of HDL in obese man [119]. Glycemic control is beneficial to lipid control, especially the level of triglycerides. In many diabetic patients, their lipid abnormalities are unable to be normalized by lifestyle intervention alone. Pharmacological management is indicated for lipid disorders in these patients.

Hydroxymethylglutaryl (HMG)-CoA Reductase Inhibitors (Statins)

Statins are most commonly used cholesterol lowering agents in diabetic patients. Statins inhibit the synthesis of cholesterol and effectively reduce the level of LDL cholesterol. Treatment with statins substantially reduces the levels of triglycerides, but relatively weak in increasing the levels of HDL cholesterol [21]. Several large scale randomized controlled trials demonstrated that statins effectively reduced cardiac events and mortality in patients with CAD or diabetes [120-124]. In the Scandinavian Simvastatin Survival Study (4S), simvastatin reduced serum lipids in diabetic patients and non-diabetic patients in similar extents. Simvastatin treatment reduced ischemic events by 55% in diabetic patients [120]. Pravastatin successfully reduced coronary events in diabetic patients in CARE (Cholesterol And Recurrent Events) trial [121]. The cardiac protective effect of statins has also been detected in patients with normal cholesterol levels [125]. Recent studies in our group demonstrated that simvastatin treatment significantly reduced the plasma levels of PAI-1 and prothrombin fragment 1+2 (F1+2) in type 2 DM patients. The levels of PAI-1, but not F1+2, correlated with total or LDL cholesterol in the patients [126]. The results suggest that statins may provide cardiac protective effects in diabetic patients through cholesterol-dependent and non-cholesterol-dependent mechanisms. The pleotropic effects of statins may result from their inhibition on the isoprenylation of signaling mediators in vascular cells [127]. The main adverse effect of statins is myopathy, which is potentially serious in patients who simultaneously administrate other medications interfering the same subtype of P450 enzymes [128].

Ezetimibe

Ezetimibe is an inhibitor of cholesterol absorption in intestine tract by suppressing Niemann-Pick C1-like 1 protein (NPC1L1) at the apical surface of enterocytes [129]. Ezetimibe alone at 10 mg/d decreases 17% of LDL-

cholesterol in hypercholesterolemic patients with no significant difference in adverse effects compared to placebo [130]. It may be an alternative for individuals who are intolerant to statins. The combination of treatment with ezetimibe and a statin offers additive effect on cholesterol lowering, which may be considered for patients with severe hypercholesterolemia failing to achieve target level of cholesterol by statin alone [131].

Peroxisome Proliferator-Activated Receptor (PPAR) Agonists

PPAR family members, PPAR- α , - δ and - γ , contain a ligand binding domain and a DNA binding domain. During ligand activation, PPARs form complex with retinoic X receptor (RXR) and bind to PPAR responsive element in target genes to regulate the transcription of the genes [132]. PPAR- α and PPAR- γ agonists have been used in clinical practice [133]. Fibrates, including gemfibrozil and bezafibrate, are introduced in 1970s as lipid lowering agents. They have been found later as PPAR- α ligands. In Veterans Administration HDL Cholesterol Intervention Trial (VA HIT), gemfibrozil decreased 31% of triglycerides, increased 6% of HDL cholesterol without significant change in LDL-cholesterol, which resulted in 22% reduction in cardiovascular outcome compared to placebo group after 5.1 years [134]. The results of Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) suggest that bezafibrate has similar lipid lowering profile and reduced coronary events in post-myocardial infarction men [135]. PPAR- γ agonists restore insulin sensitivity, promote FFA uptake in adipose tissue, increase glucose transport in muscle and liver, and potentially affect inflammation [132]. Troglitazone, the prototype of PPAR- γ agonists, reduced triglycerides and fasting glucose, but it was discontinued due to hepatotoxicity [136]. Pioglitazone and rosiglitazone have better safety profiles than troglitazone. In patients of diabetes, pioglitazone and rosiglitazone improve glucose control, reduce FFA and triglyceride. The PPAR- γ agonists increase HDL-cholesterol, but also LDL-cholesterol, in diabetic patients. However, no significant change was found in the total cholesterol and HDL-cholesterol ratio in these patients [137, 138]. Ongoing trials are investigating the impact of PPAR- α/γ agonists on glycemic control, lipid profile and inflammation markers in diabetic patients.

Medications Increasing HDL-Cholesterol

The levels of HDL-cholesterol negatively correlate with cardiovascular outcomes, and become a potential therapeutic target. Statins and PPAR agonists only mildly increase HDL-cholesterol levels. Nicotinic acid considerably increases HDL-cholesterol (up to 34%), but it often causes rash and increases blood glucose and glycosylated hemoglobin in 16% and 21% in type 2 DM patients [139]. CETP inhibitors greatly increase HDL-cholesterol (up to 50%) and reduced the levels of triglyceride-rich lipoproteins [140]. Apo-AI mimetic peptide or delipidated HDL may be potential alternatives for raising HDL level in some patients, but they are still in experimental or early phases of clinical trials [141]. The efficacy and safety of these newer treatments for increasing HDL levels required extensive studies.

CONCLUSION

Diabetic lipid disorders are characterized by hypertriglyceridemia, increased small dense LDL, reduced HDL-cholesterol, and postprandial hyperlipidemia. Dyslipidemia in diabetes is a consequence of absolute or relative insulin deficiency and subsequent disorders in the activity of lipid metabolism enzymes or transporters. Diabetic dyslipidemia increases the risk for the patients to develop macro- or microvascular complications through their effects on endothelial function, inflammation, coagulation, fibrinolysis and platelet activation. First line of the management of dyslipidemia in diabetic patients with lipid disorders is lifestyle intervention and glucose control. For diabetic patients whose dyslipidemia are unable to control by glucose/style intervention, active treatment with statins or PPAR agonists is recommended.

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