

Dyslipidemia, Kidney Disease, and Cardiovascular Disease in Diabetic Patients

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■ Abstract

This article reviews the relationship between dyslipidemia, chronic kidney disease, and cardiovascular diseases in patients with diabetes. Diabetes mellitus is associated with complications in the cardiovascular and renal system, and is increasing in prevalence worldwide. Modification of the multifactorial risk factors, in particular dyslipidemia, has been suggested to reduce the rates of diabetes-related complications. Dyslipidemia in diabetes is a condition that includes hypertriglyceridemia, low high-density lipoprotein levels, and increased small and dense low-density lipoprotein particles. This condition is associated with higher cardiovascular risk and mortality in diabetic patients. Current treatment guidelines focus on lowering the low-density lipoprotein cholesterol level; multiple trials have confirmed the cardiovascular benefits of treatment with statins. Chronic kidney disease also contributes to dyslipidemia, and dyslipidemia in turn is related to the occurrence and progression of diabetic neph-

ropathy. Different patterns of dyslipidemia are associated with different stages of diabetic nephropathy. Some trials have shown that treatment with statins not only decreased the risk of cardiovascular events, but also delayed the progression of diabetic nephropathy. However, studies using statins as the sole treatment of hyperlipidemia in patients on dialysis have not shown benefits with respect to cardiovascular risk. Diabetic patients with nephropathy have a higher risk of cardiovascular events than those without nephropathy. The degree of albuminuria and the reduction in estimated glomerular filtration rate are also correlated with the risk of cardiovascular events. Treatment with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers to reduce albuminuria in diabetic patients has been shown to decrease the risk of cardiovascular morbidity and mortality.

Keywords: type 2 diabetes · dyslipidemia · chronic kidney disease · cardiovascular disease

1. Introduction

D iabetes mellitus is a critical health issue worldwide. According to data from the International Diabetes Federation, 371 million adults were diagnosed with diabetes, and an estimated 4.8 million people died of the disease in 2012 [1]. The number of adults with diabetes may increase to 552 million in 2030 [1]. Type 2 diabetes (T2D) accounts for more than 90% of all cases of diabetes and, in the majority of patients, is diagnosed between 40 and 60 years of age. The social

and economic burden of diabetes is a major global problem, especially in developing countries.

Patients with diabetes have much higher morbidity and mortality than the general population because of the complications associated with the disease. Atherosclerotic cardiovascular disease, which manifests clinically as coronary heart disease, cerebral vascular disease, and other peripheral artery diseases (PAD), is the most common macrovascular complication in diabetic patients. In the Framingham Study, the incidence of atherosclerotic disease was 2-fold to 3-fold higher in pa-

tients with diabetes compared to healthy subjects. [2]. In the Multiple Risk Factor Intervention Trial (MRFIT), the mortality rate of cardiovascular disease was 3 times higher in patients with diabetes than in normal subjects. [3]. In Taiwan, cardiovascular disease is the second leading cause of death in patients with diabetes [4]. Diabetes has been recognized as a cardiovascular disease equivalent [5-8]. The higher incidence of cardiovascular disease in diabetic patients may be related to endothelial damage caused by hyperglycemia, traditional risk factors (smoking, dyslipidemia, and hypertension), or disturbed metabolism (oxidative stress, decreased nitric oxide production, and chronic inflammation) [9].

More than one-third of diabetic patients experience microvascular complications such as retinopathy, nephropathy, and neuropathy [10, 11]. Metabolic abnormalities (hyperglycemia, accumulation of advanced glycation end products, oxidative stress) [12] and vasoactive renal factors (renin-angiotensin system and other vasoconstrictors) [13] play a role in the development of diabetic nephropathy. The classic characteristics of diabetic nephropathy include hypertension, proteinuria, and impairment of renal function. Diabetic nephropathy is the major cause of end-stage renal disease, and reports from both the National Health and Nutrition Examination Survey (NHANES) and the United States Renal Data System (USRDS) have shown a steadily increasing prevalence of diabetic nephropathy in the United States [14, 15]. A global study showed that the incidence rate of albuminuria in T2D is higher in Asian than in Caucasian patients (55% vs. 41%) [16]. Patients with T2D and chronic kidney disease (CKD) have a significantly higher mortality rate than those without nephropathy [17].

Dyslipidemia is common in diabetic patients. Typical manifestations of diabetes-related dyslipidemia include fasting and postprandial hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C) levels, increased small and dense low-density lipoprotein (LDL) particles, and elevated apolipoprotein B (ApoB) levels [18-20]. All of these lipid abnormalities are highly atherogenic and determinants of cardiovascular disease. A higher prevalence of dyslipidemia is noted in patients with CKD caused by abnormalities of lipid metabolism. Impaired renal function is also an independent predictor of cardiovascular events and risk of death [21]. In the World Health Organization Multinational Study of Vascular Disease in Diabetes, both serum cholesterol level and proteinuria were strong predictors of cardiovascular

Abbreviations:

ACCORD - Action to Control Cardiovascular Risk in Diabetes
 ADVANCE - Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation
 AGE - advanced glycation end-product
 AIM-HIGH - Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes
 ApoB - apolipoprotein B
 AURORA - A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events
 CARDS - Collaborative Atorvastatin Diabetes Study
 CKD - chronic kidney disease
 CVD - cardiovascular disease
 4D - Die Deutsche Diabetes Dialyse Studie
 DAIS - Diabetes Atherosclerosis Intervention Study
 DCCT - Diabetes Control and Complications Trial
 EDIC - Epidemiology of Diabetes Interventions and Complications
 eGFR - estimated glomerular filtration rate
 ETDRS - Early Treatment Diabetic Retinopathy Study
 KDOQI - Kidney Disease Outcomes Quality Initiative
 KEEP - Kidney Early Evaluation Program
 FFA - free fatty acid
 FIELD - Fenofibrate Intervention and Event Lowering in Diabetes
 GREACE - GREek Atorvastatin and Coronary-heart-disease Evaluation
 HbA1c - hemoglobin A1c
 HDL - high-density lipoprotein
 HDL-C - high-density lipoprotein cholesterol
 HOPE - Heart Outcome Prevention and Evaluation
 HPFS - Health Professionals Follow-Up Study
 HPS - Heart Protection Study
 JUPITER - Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
 LDL - low-density lipoprotein
 LDL-C - low-density lipoprotein cholesterol
 LPL - lipoprotein lipase
 MICRO-HOPE - Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE
 MRFIT - Multiple Risk Factor Intervention Trial
 NCEP-ATP III - National Cholesterol Education Program Adult Treatment Panel III
 NHANES - National Health and Nutrition Examination Survey
 PAD - peripheral artery disease
 RAAS - renin-angiotensin-aldosterone system
 RENAAL - Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
 SHARP - Study of Heart and Renal Protection
 T2D - type 2 diabetes
 TGF-beta - transforming growth factor beta
 TNT - Treating to New Targets
 USRDS - United States Renal Data System
 VA-HIT - Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial
 VLDL - very low-density lipoprotein
 VLDL-C - very low-density lipoprotein cholesterol
 WHO MSVDD - World Health Organization Multinational Study of Vascular Diseases in Diabetes

disease mortality, fatal and non-fatal myocardial infarction, and stroke [22]. Greater cardiovascular risk in patients with diabetic nephropathy may partly be due to the atherogenic lipoprotein changes associated with renal failure. In addition to adverse effects on the cardiovascular system, dyslipidemia may also correlate with progression of diabetic nephropathy.

Because of the higher incidence of CKD and cardiovascular disease in patients with diabetes, we review the relationship between dyslipidemia, CKD, and cardiovascular diseases in patients with diabetes.

2. Diabetes and dyslipidemia

The pathogenesis of diabetic dyslipidemia is complex. Insulin could mediate the uptake of free fatty acids (FFAs) by striated muscle and adipose tissue. Therefore, increased insulin resistance would result in increased levels of FFAs delivered to the liver, giving rise to overproduction of very low-density lipoprotein (VLDL) and to increased very low-density lipoprotein cholesterol (VLDL-C) concentration, with the clinical manifestation of hypertriglyceridemia. Decreased lipoprotein lipase (LPL) activity also leads to an accumulation of triglyceride-rich lipoproteins in the plasma. VLDL-C could stimulate the exchange of triglycerides to cholesterol ester from HDL and LDL, which causes a higher catabolic rate of HDL and conversion of LDL to small and dense LDL [23]. The small and dense LDL could preferentially penetrate the arterial wall and is highly susceptible to glycation and oxidation, which may lead to atherosclerosis. Insulin resistance can also cause overproduction of ApoB-containing lipoprotein from the liver, manifesting as hepatic VLDL overproduction [24, 25].

Because of the increased risk of and higher mortality rate from cardiovascular disease in diabetic patients, interventions to decrease macrovascular events are important [2, 26]. Atherogenic dyslipidemia is a precipitating factor for higher risk of cardiovascular disease in patients with T2D. In the Steno-2 study, a multifactorial intervention that included lowering hemoglobin A1c (HbA1c) to less than 6.5%, blood pressure control, treatment of dyslipidemia, and anti-platelet therapy improved cardiovascular outcomes compared with standard therapy [27]. In 2012, the American Diabetes Association recommended statin therapy in addition to lifestyle modification for those at high risk for cardiovascular disease regardless of baseline lipid levels [28]. The guidelines of the Na-

tional Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) emphasized that dyslipidemia is one of the major causes of higher cardiovascular risk in patients with diabetes [29] and suggested that LDL particles are highly atherogenic. This means that cholesterol-lowering therapy should be primarily focused on decreasing LDL-cholesterol (LDL-C) levels. Multiple landmark trials have shown that lowering LDL-C levels could lead to major clinical benefits in reducing cardiovascular events in patients with T2D. The Strong Heart Study showed that when LDL-C level increased by 10 mg/dl, the risk of cardiovascular disease increased by 12% in American Indian patients with diabetes [30]. In the Treating to New Targets (TNT) study, lowering LDL-C levels to 77 mg/dl led to a 25% reduction in major cardiovascular events in patients with diabetes and coronary heart disease compared with the use of a target LDL-C level of 100 mg/dl [31]. A meta-analysis of 18,686 patients with diabetes in 14 randomized trials of treatment with statins showed that there was a reduction of 9% in all-cause mortality, of 21% in major vascular events, and of 22% in myocardial infarction or coronary death per mmol/l reduction in LDL-C level [32]. However, diabetic patients treated with statins still have a higher residual risk of cardiovascular events than non-diabetic patients. Reduction of LDL-C level alone cannot eliminate all of the excess cardiovascular risk in patients with diabetes.

Many prospective epidemiologic studies have reported a positive relationship between serum triglyceride levels and incidence of coronary heart disease, especially in patients with diabetes [33, 34]. Lipoprotein remnants are triglyceride-rich and atherogenic, and higher levels of atherogenic remnant lipoproteins could increase the risk of coronary heart disease when triglyceride levels are ≥ 200 mg/dl [35]. The most accessible measure of lipoprotein remnants is VLDL-C. As a result, VLDL-C could be combined with LDL-C to increase prediction of cardiovascular risk, especially in patients with a high triglyceride level. The NCEP-ATP III guidelines suggested the use of non-HDL-C (sum of VLDL-C and LDL-C) as a secondary target for subjects with a triglyceride level > 200 mg/dl [36]. Fibrates are the most effective medication to lower triglyceride levels; both the Helsinki Heart Study and the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) showed cardiovascular benefit in non-diabetic subjects treated with fibrates compared with placebo. However, randomized con-

trolled trials failed to show additional benefit for cardiovascular events with fibrate therapy in patients with T2D. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study of patients with T2D showed that treatment with fenofibrate as additive therapy with a statin did not reduce the risk of major coronary events. However, fewer non-fatal myocardial infarctions and revascularizations were noted, leading to a decreased number of total cardiovascular events [37]. Most participants in the FIELD study, including both the fenofibrate treatment group and the placebo group, were also treated with a statin.

There is no consensus regarding combination treatment with lipid-lowering agents in diabetic patients. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, combination therapy with a fibrate plus a statin was compared with treatment with a statin alone in patients with T2D. The results showed no significant difference between the 2 groups in cardiovascular death, non-fatal myocardial infarction, or stroke. However, subgroup analysis of the ACCORD study showed that fibrate therapy in addition to a statin may decrease the risk of cardiovascular disease in patients with triglyceride levels >240 mg/dl and HDL-C levels <34 mg/dl [38].

Niacin is effective for raising HDL-C levels. In the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study, although the addition of niacin to treatment with a statin could significantly increase HDL-C levels and decrease triglyceride levels, there was no cardiovascular benefit in patients treated with niacin [39]. The Heart Protection Study 2 THRIVE trial was a large randomized study that included patients with a total cholesterol level <135 mg/dl (on simvastatin therapy with or without ezetimibe) before randomization. Addition of extended-release niacin plus laropiprant in the treatment group reduced LDL-C levels and increased HDL-C levels compared with the placebo group. However, the primary outcome of major vascular events (non-fatal myocardial infarction, coronary heart disease, stroke, arterial revascularization) was not different between the 2 groups [40].

The association between treatment with statins and new-onset diabetes is of concern. The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), which was published in 2008, showed a higher incidence of diabetes in the rosuvastatin treatment group [41]. Such an association has also been confirmed by some cohort studies and meta-

analysis [42-44]. In February 2012, the Food and Drug Administration changed the safety label of statins to indicate the risk of increased HbA1c and fasting serum glucose levels [45]. However, the benefit of a statin in decreasing the risk of cardiovascular disease may outweigh the risk of elevated blood glucose levels in diabetic patients.

3. Correlation between dyslipidemia and diabetic nephropathy

As a result of dysregulation of lipid metabolism, CKD alone could lead to dyslipidemia [46]. In diabetic patients with CKD, dyslipidemia could be aggravated by hyperglycemia and insulin resistance [47]. Reduced endothelial cell LPL expression and activity are also noted in patients with CKD [48]. These abnormalities can lead to delayed catabolism of ApoB containing triglyceride-rich lipoproteins. Increased levels of Apo-CIII, which are commonly found in patients with microalbuminuria, would inhibit LPL activity and suppress the removal of ApoB [46]. Hepatic lipase can hydrolyze triglycerides and phospholipid in chylomicron remnants and HDL [48]. Decreased activity and expression of hepatic lipase in CKD have been confirmed in animal models [49]. LDL receptor-related protein and VLDL-C receptor messenger RNA are downregulated in animals with CKD [50, 51]. All of these abnormalities can lead to accumulation of atherogenic chylomicrons and VLDL-C remnants. In patients with CKD, Apo-AI concentrations are decreased as a result of reduced hepatic synthesis and increased catabolism. Low Apo-AI concentration, decreased binding capacity with adenosine triphosphate-binding cassette transporter 1, and decreased lecithin-cholesterol acyltransferase activity all result in decreased synthesis of HDL [46, 48, 52]. Total cholesterol and LDL-C levels are usually within normal limits.

Many epidemiologic studies examine the effect of albuminuria and renal function on dyslipidemia in diabetic patients. A study of 200 Japanese patients with T2D investigated the lipoprotein changes in diabetic nephropathy, and the results showed that VLDL-C level did not differ at different stages of nephropathy. In patients with increased serum creatinine levels, higher intermediate-density lipoprotein cholesterol and lower HDL-C levels were noted. There were no differences in LDL-C levels in patients with diabetes and those without diabetes [53]. A large prospective study using the Hong Kong Diabetes Registry showed that increased macroalbuminuria was a risk factor for developing elevated total cholesterol and LDL-

C levels. A decreased estimated glomerular filtration rate (eGFR), commencing from 110 ml/min/1.73 m², could predict reduced HDL-C levels [54]. A small Japanese study confirmed the increased ApoB₄₈ and small dense LDL levels in patients with diabetic nephropathy; the increase in ApoB₄₈ level was higher in patients with macroalbuminuria than in patients with microalbuminuria [55].

There is also increasing evidence for the association of dyslipidemia and the occurrence and progression of renal disease in both diabetic and non-diabetic patients [56-59]. There are several mechanisms by which dyslipidemia could lead to diabetic nephropathy. For example, triglyceride-rich lipoprotein could stimulate the activation of the transforming growth factor-beta (TGF- β) pathway. TGF- β subsequently promotes the production of reactive oxygen species, leading to glomerular damage. Activation of TGF- β also increases matrix deposition in the tubulointerstitium and mesangium [60]. In addition to the TGF- β pathway, triglyceride-rich lipoprotein can activate monocytes and disrupt cellular glycocalyx, causing increased permeability in the glomerulus [61]. Oxidized lipoprotein can inhibit nitric oxide-mediated vasodilation, modulate mesangial cell proliferation, and increase monocyte chemoattractant expression, which all contribute to glomerular injury [62, 63]. These adverse effects can be reversed by HDL. However, a reduced HDL-C level in patients with CKD may precipitate kidney injury.

The Health Professionals Follow-Up Study (HPFS) and Atherosclerosis Risk in Communities Study showed that hypertriglyceridemia and a decreased HDL-C level, which were characteristic of dyslipidemia in patients with diabetes, were associated with a decreased glomerular filtration rate in individuals with T2D [56, 64]. In some prospective studies, hypercholesterolemia predicts the development of diabetic nephropathy [65-67]. In the Early Treatment Diabetic Retinopathy Study (ETDRS), hypertriglyceridemia was a risk factor for end-stage renal disease in patients with T2D [67]. The World Health Organization Multinational Study of Vascular Diseases in Diabetes (WHO MSVDD) also showed that triglyceride level was a risk factor for renal failure in patients with T2D [68]. Hypertriglyceridemia and hyper-ApoB level may play a role in the onset of albuminuria in patients with T2D [69, 70]. In a cross-sectional study involving Chinese patients with T2D without renal dysfunction, closer correlation between non-HDL-C and urinary albumin excretion rates

was noted than with other lipid parameters [71]. There are diverse results in the association between the pattern of dyslipidemia and diabetic nephropathy, possibly because the different types of dyslipidemia are associated with different stages of diabetic nephropathy. In a study of 549 Taiwanese patients with T2D, differential dyslipidemia was observed in different stages of microalbuminuria and macroalbuminuria [72]. ApoB levels increased in the microalbuminuria stage, whereas lipoprotein(a) levels increased in the macroalbuminuria stage [72]. However, only levels of triglycerides progressively increased with albuminuria, from normoalbuminuria to microalbuminuria and to macroalbuminuria [72]. In the Kidney Early Evaluation Program (KEEP) study of diabetic patients with CKD stage 3 to 5, only an elevated HDL-C level was associated with decreased odds of microalbuminuria [73]. There was no statistical significance between the albumin excretion rate and other lipid profiles in patients with T2D [73].

Because dyslipidemia may play a role in the progression of diabetic nephropathy, treatment with lipid-lowering agents may be beneficial for renal outcomes besides their beneficial effects on CVD in patients with T2D [74]. In animal models of diabetes, treatment with a statin decreases lipid peroxidation, increases antioxidant enzyme levels, reduces accumulation of advanced glycation end-products, and reverses podocyte injury [75-77]. A meta-analysis of diabetic and non-diabetic patients with renal disease demonstrated that control of dyslipidemia with a statin has a beneficial effect on renal outcomes in terms of improved glomerular filtration rate (GFR) and proteinuria [78]. In the MRC/BHF Heart Protection Study (HPS), a smaller decrease in eGFR during follow-up was noted in the simvastatin treatment group than in the placebo group, especially in diabetic patients [79]. In the Collaborative Atorvastatin Diabetes Study (CARDS), treatment with atorvastatin improved renal function deterioration in T2D, especially in patients with albuminuria [80]. A prospective analysis of patients with T2D in Hong Kong also confirmed the benefit of treatment with a statin to reduce diabetic nephropathy in T2D [81]. In the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study, treatment with atorvastatin increased eGFR in both diabetic and non-diabetic patients [82].

Beside statins, fibrates may also produce renal benefits in diabetic patients. Results from the Diabetes Atherosclerosis Intervention Study (DAIS)

showed that treatment with fenofibrate decreased the risk of developing microalbuminuria [83]. In the FIELD study, subjects in the fenofibrate group showed a slower progression of albuminuria than those in the placebo group [37]. However, statin therapy in diabetic patients undergoing dialysis is not recommended in the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline [84]. The results of Die Deutsche Diabetes Dialyse Studie (4D), A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), and a subgroup analysis of the Study of Heart and Renal Protection (SHARP) all failed to show a significant benefit of statin treatment on primary cardiovascular outcomes in patients on dialysis [85-87]. On post-hoc analysis of diabetic participants in the AURORA study, a greater risk of hemorrhagic stroke was noted in the rosuvastatin treatment group, although the risk of cardiac death or non-fatal myocardial infarction was decreased [88]. However, in SHARP, combination therapy with simvastatin 20 mg plus ezetimibe 10 mg daily reduced major atherosclerotic events in patients with or without dialysis intervention [89].

4. Correlation between renal disease and cardiovascular disease

In the 2007 European Society of Cardiology and the European Atherosclerosis Society Guidelines, CKD is acknowledged as a CVD risk equivalent [90]. Both abnormal urinary albumin excretion and decreased eGFR are strong predictors of CVD [91], and the correlation would be more prominent in diabetic patients [92]. In diabetic patients with microalbuminuria, increased subclinical atherosclerosis is confirmed by higher values for brachial-ankle pulse wave velocity and intima-media thickness [93]. There are many pathological mechanisms linking a higher risk of CVD and mortality in diabetic patients with kidney disease. Firstly, hypertension and dyslipidemia, which are traditional risk factors for CVD, are common in diabetic patients with albuminuria. Other non-traditional risk factors, such as chronic inflammation, insulin resistance, endothelial dysfunction, and atherogenic lipoprotein changes, also play a role in pathogenesis. Multiple biochemical parameters such as von Willebrand factor, plasminogen activator inhibitor type 1, soluble vascular cell adhesion molecule 1, intercellular adhesion molecule 1, plasma endothelin 1, C-reactive protein, and fibrinogen are associated with microalbuminuria

[64, 94-98]. In the Hoorn study, both lower eGFR and greater urinary albumin excretion rate were independently associated with greater arterial stiffness [99]. Microalbuminuria had a linear association with impaired endothelium-dependent, flow-mediated vasodilatation of the brachial artery and increased circumferential wall tension and wall stress in the carotid artery in individuals with and without diabetes in the same study [100, 101]. All of these abnormalities explain the association between microalbuminuria and atherosclerosis through mechanisms of chronic inflammation, endothelial dysfunction, and diffuse vascular damage. Compared with diabetic patients with normoalbuminuria, more severe insulin resistance with higher levels of FFAs was noted in diabetic patients with albuminuria. Yu *et al.* confirmed the association between impaired flow-mediated vasodilatation and peripheral insulin resistance [94].

Many epidemiologic studies have demonstrated the relationship between CKD and CVD in diabetic patients [92]. A study in Hong Kong showed that among various components of metabolic syndrome, albuminuria is the strongest predictor of CVD mortality in Chinese patients with T2D [102]. A review of studies of patients with T2D showed a 2-fold increase in CVD morbidity or mortality in patients with microalbuminuria compared with those with normoalbuminuria [103]. The Heart Outcome Prevention and Evaluation (HOPE) study showed that any degree of albuminuria is a strong predictor of CVD outcomes in both diabetic and non-diabetic patients. The major CVD risk (myocardial infarction, stroke, cardiovascular death) increases by 5.9% for every 0.4 mg/mmol increase in urinary albumin excretion rate. In diabetic individuals, the adjusted relative risk (patients with microalbuminuria vs. those without microalbuminuria) for major CVD risk and hospitalization for congestive heart failure was 1.97 and 3.70, respectively [104]. In a study of 914 patients who underwent coronary angiography, there was a significant correlation of albuminuria and the severity of angiographically determined coronary atherosclerosis in both diabetic and non-diabetic patients [105]. In Chinese patients with T2D, deteriorated glomerular filtration rate could predict a higher risk of cardiovascular end points and all-cause mortality after adjustment for albuminuria [106]. In the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study, which included 10,640 patients with T2D, a 10-fold elevation of baseline urinary albumin/creatinine ratio resulted in a 2.48-fold increased risk of cardiovascular

events compared with baseline. Every 50% reduction in baseline eGFR value increased the risk of cardiovascular events 2.20-fold. There was no interaction between albuminuria and decreased eGFR in this study. In patients with both macroalbuminuria and stage 3-5 CKD, the risk of cardiovascular events increased 3.2-fold [107]. Albuminuria is also associated with ankle-brachial index in an inverse pattern [93] and with peripheral artery disease [108, 109].

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are proposed in the treatment of diabetes with microalbuminuria or macroalbuminuria [28]. Because albuminuria and CKD are closely correlated with cardiovascular disease risk, medications that could lower the urinary albumin excretion rate are expected to have cardiovascular benefits. In the HOPE and Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE (MICRO-HOPE) studies, treatment of diabetic patients with ramipril reduced the risk of diabetic nephropathy, stroke, cardiovascular death, revascularization, and total mortality. In a subgroup analysis, the effect was more prominent in patients with microalbuminuria and the primary outcome effect persisted after adjustment for changes in blood pressure [110, 111]. The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, a double-blind randomized trial of 1513 patients with T2D, showed a positive correlation between baseline albuminuria and the risk of the CVD end point or heart failure. Treatment with losartan could reduce proteinuria and risk reduction for end-stage renal disease [112]. Further analysis showed that every 50% reduction in albuminuria resulted in an 18% reduction in cardiovascular risk and a 27% reduction in heart failure risk [113].

In the Losartan Intervention for Endpoint reduction in hypertension (LIFE) study, losartan was compared with atenolol in relation to its blood pressure lowering effect and reduction in cardiovascular morbidity and mortality in diabetic patients with hypertension and left ventricular hypertrophy. Even with the same anti-hypertensive effect, greater risk reduction in cardiovascular mortality, stroke, and myocardial infarction was noted in the losartan treatment group [114, 115]. A post-hoc analysis combining the RENAAL study and the Irbesartan in Diabetic Nephropathy Trial showed that each decrement in log albuminuria would lead to an approximately 15% risk reduction in cardiovascular events [116]. The association between urinary albumin/creatinine ratio and pe-

ripheral artery disease also became insignificant in patients treated with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, implying that the use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers might lower the risk of peripheral artery disease [109].

5. Correlation between glucose control with lipid levels, diabetic nephropathy, and cardiovascular complications

Glycemic control is important for all diabetic patients, with better blood glucose control affecting microvascular and macrovascular outcomes in patients with diabetes. The United Kingdom Prospective Study, which included 5102 patients with newly diagnosed T2D, showed that intensive blood glucose control (HbA1c of 7.0% versus 7.9%) decreased the risk of microvascular disease (relative risk reduction: 25%) and microalbuminuria (relative risk reduction: 33%) over a median follow-up of 10 years [117]. There was a trend toward decreased cardiovascular events with intensive blood glucose control, but this did not reach statistical significance (relative risk reduction: 16%; $p = 0.052$). However, a continued reduction in microvascular risk (relative risk reduction: 24%) and a significant reduction in myocardial infarction (relative risk reduction: 15%, $p = 0.01$) were noted during 10 years of post-trial follow-up, despite an early loss of glycemic differences [118].

In the Diabetes Control and Complications Trial (DCCT, 1982-1993) and the Epidemiology of Diabetes Interventions and Complications (EDIC, 1994-2006) follow-up study in type 1 diabetes, intensive glucose therapy decreased the risk of progression to microalbuminuria and overt nephropathy [119]. There was no statistically significant difference in the DCCT between the 2 groups (HbA1c of 7.2% versus 9.1%) with regard to cardiovascular disease. However, the benefit of intensive blood glucose control on cardiovascular outcomes was noted with 17 years of follow-up and observation in the EDIC study; the risk of cardiovascular disease (non-fatal myocardial infarction, stroke, death from cardiovascular disease, confirmed angina, and need for coronary artery revascularization) was reduced by 42% and the risk of non-fatal heart attack, stroke, or death from cardiovascular causes was reduced by 57% [117].

In the ADVANCE study, further reduction of HbA1c to 6.5% compared with 7.3% led to a 10%

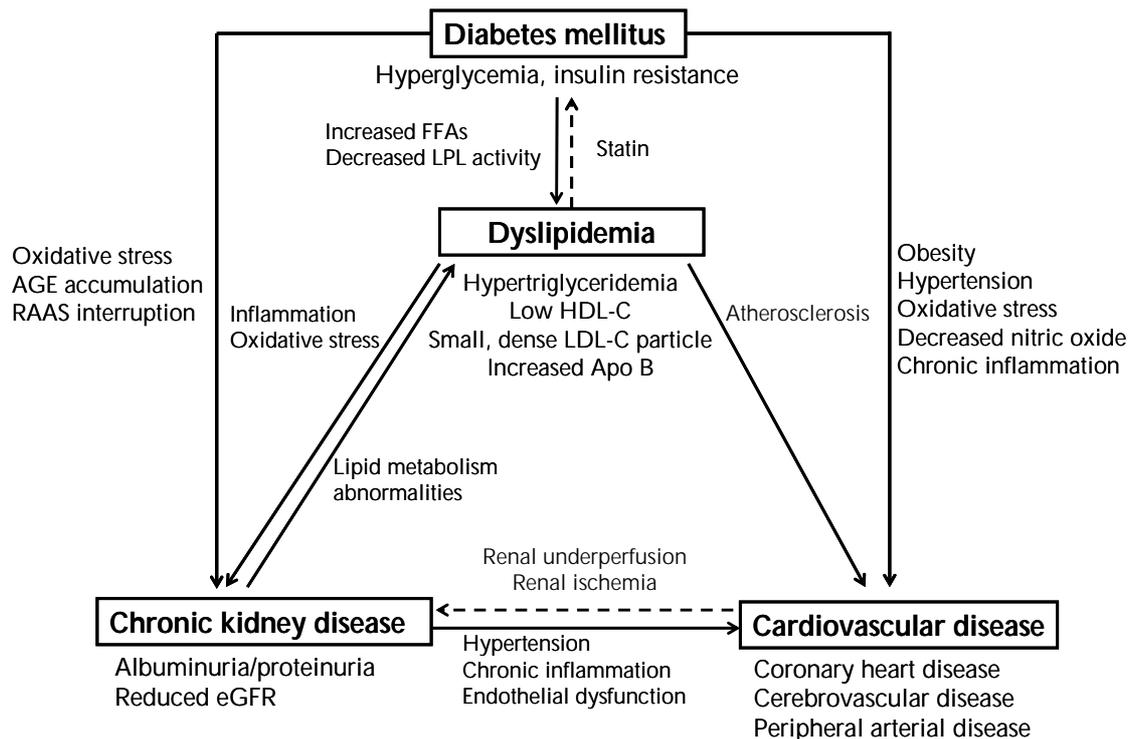


Figure 1. Relationship between dyslipidemia, chronic kidney disease, and cardiovascular disease in diabetes mellitus. AGE - advanced glycation end-product, Apo B - apolipoprotein B, eGFR - estimated glomerular filtration rate, FFA - free fatty acid, HDL-C - high-density lipoprotein cholesterol, LDL-C - low-density lipoprotein cholesterol, LPL - lipoprotein lipase, RAAS - renin-angiotensin-aldosterone system.

relative risk reduction in the combined outcome of major macrovascular and microvascular events, especially nephropathy [120]. These studies suggested that intensive glucose control is most effective when implemented early in the course of diabetes. In the ACCORD study, which included patients with T2D and established CVD or multiple risk factors, the risk of major cardiovascular events was not reduced in the group that received more intensive therapy (HbA1c of 6.4%) over 3.5 years of follow-up [121].

These results suggested that intensive blood glucose control reduces the risk of diabetic nephropathy and probably reduces CVD events as well during long-term follow-up. Better blood glucose control would improve dyslipidemia because of the mechanism of diabetic dyslipidemia. A trial of 1150 patients with T2D showed a close relationship between triglyceride level and fasting plasma glucose level and HbA1c [33].

6. Conclusions

In summary, there is a close correlation between dyslipidemia, CKD, and CVD in patients with T2D. Diabetes mellitus is a strong risk factor for CKD and CVD. Dyslipidemia is common in diabetic patients and diabetic dyslipidemia is strongly correlated with diabetic nephropathy and CVD. The relationship between dyslipidemia, diabetic nephropathy, and CVD in patients with T2D is summarized in **Figure 1**. Because treatment of dyslipidemia with a statin may delay the progression of diabetic nephropathy and reduce cardiovascular risk, early identification and aggressive treatment, if needed, is important in all diabetic patients without contraindications or end-stage renal disease.

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