Treatment and impact of dyslipidemia in diabetic nephropathy

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REVIEW ARTICLE

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Treatment and impact of dyslipidemia in diabetic nephropathy

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Abstract Recent epidemiological research revealed that dyslipidemia is a risk factor for development and progression of diabetic nephropathy. Results from interventional studies revealed the possibility that anti-hyperlipidemic agents have a better effect on diabetic nephropathy through improvement of albuminuria and loss of renal function. In addition, dyslipidemia may be a consequence of albuminuria and renal dysfunction, thereby perpetuating kidney damage. Today, the proportion of diabetic patients receiving statins is increasing due to their beneficial effect on cardiovascular mortality. However, treatment for patients should be determined based on consideration of the risk and benefit of the treatment. More insight into the pathogenesis of diabetic nephropathy and the effects of life-style changes is required.

Keywords Diabetic nephropathy · Dyslipidemia · Cardiovascular disease · End-stage renal disease

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Introduction

In the past, epidemiological research in diabetes has found that albuminuria and renal dysfunction are dominant risk factors for the progression of diabetic nephropathy. Some interventional studies have revealed that strict glycemic control reduces the risk of development and progression of albuminuria [1, 2].

It is a crucial fact that diabetic patients are at high risk of cardiovascular events. To prevent these events, dyslipidemia should be carefully controlled because it is one of the well-known risk factors. Statins and fibrates are representative drugs for dyslipidemia. Besides reducing plasma cholesterol levels they are thought to have many pleiotropic effects including improvement of endothelial function and inflammation [3, 4]. However, treatment of patients with dyslipidemia is complicated because it is not a simple metabolic disorder but closely related to the patient's lifestyle. For this reason, lowering the level of cholesterol will not always result in a reduction of the risks.

Here, we focus on the treatment and impact of dyslipidemia on the progression of diabetic nephropathy.

Dyslipidemia as a complication of diabetic nephropathy

One cross-sectional study implied that patients with diabetic nephropathy had significant increases in triglycerides and total cholesterol levels, reduced levels of apolipoprotein A (ApoA)-I and ApoA-II, and increased levels of ApoC-II and ApoC-III [5]. Other cross-sectional studies of patients from the Diabetic Control and Complications Trial/Epidemiology of Diabetic Interventions and Complications study group revealed that high levels of triglycerides, low-density lipoprotein (LDL) cholesterol, total

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cholesterol, and ApoB are associated with albuminuria [6]. ApoB is thought to be related to cardiovascular events in some studies [7, 8]. In this way, the studies revealed the relationships between lipid profiles and diabetic nephropathy.

Cardiovascular events are also important complications in diabetic patients [9]. A meta-analysis reported the relationship between dyslipidemia and cardiovascular risk [10]; however, risks for diabetic patients are not well known.

Dyslipidemia and loss of renal function

The 'lipid nephrotoxicity' hypothesis was advocated by Moorhead et al. in 1982 as a description of the effect of dyslipidemia on renal dysfunction [11]. Under this hypothesis, mesangial proliferation caused by accumulation of lipoprotein into mesangial cells induces glomerulosclerosis. This theory has been updated recently including the concept of inflammation stress modifying lipid homeostasis and tissue lipid accumulation [12]. With regard to diabetes and lipids, Hartroft [13] discovered in 1954 that intraluminal fat was found in both preglomerular and postglomerular vessels of diabetics patients with Kimmelstiel–Wilson lesions. In addition to this study, a lot of basic research has discovered the mechanisms between dyslipidemia and diabetic nephropathy [14]. Studies revealed that transforming growth factor-β signaling [15], renin–angiotensin system [16], S100A8/TLR4 signaling [17], and oxidative stress [18] may play an important role in the progression of diabetic nephropathies. Concerning the development of albuminuria, the importance of the deterioration of glycocalyx, which is on the surface of endothelium, was highlighted [19]. These factors orchestrated each other, thereby perpetuating the progression of diabetic nephropathy. Further studies will be required for a better understanding of diabetic nephropathy.

Some epidemiological studies of general cohorts have elucidated the relationships between dyslipidemia and loss of renal function. The Framingham Offspring Study which consists of 1,916 general population subjects with a follow-up of 9.5 years, revealed that low high-density lipoprotein (HDL) cholesterol levels are one of the risk factors for incident albuminuria [20]. An analysis of 1,440 general Japanese cohorts that participated in the Hisayama study revealed that metabolic syndrome defined as the presence of components including high triglyceride levels and low HDL cholesterol levels are associated with a risk of developing chronic kidney disease (CKD) [21]. A study of 4,483 healthy males revealed that dyslipidemia including high total cholesterol levels, high non-HDL cholesterol levels, and low HDL cholesterol levels are associated with a risk of renal dysfunction [22].

According to these facts, dyslipidemia may be one of the potential risk factors for loss of renal functions in a healthy subject.

Relationships between dyslipidemia and progression or regression of diabetic nephropathy

The stages in diabetic renal disease were reported by Mogensen et al. [23] in 1983. According to their theory, elevated urinary albumin excretion and following persistent proteinuria are important manifestations of diabetic nephropathy, and many studies defined them as surrogate markers for end-stage renal disease.

Some cohort studies of diabetic patients have proven the risk factors associated with the progression or regression of the staging. Regarding the development of micro- and macroalbuminuria, a cohort study of 27,805 patients with type 1 diabetes followed up for 2.5 years revealed that, besides diabetes duration and glycosylated hemoglobin, dyslipidemia is a risk factor for developing albuminuria [24]. A cohort study of 574 patients with type 2 diabetes followed up for 7.8 years also revealed that, as well as high mean blood pressure and hyperglycemia, high plasma cholesterol levels are the main risk factors for development of dyslipidemia [25]. In this study, the participants with a combination of these three risk factors are a high-risk group for progression to diabetic nephropathy.

Associations between reduction of urinary albumin and dyslipidemia were reported in a cohort study of 386 patients with type 1 diabetes [26]. In this study, along with low levels of glycosylated hemoglobin and low systolic blood pressure, low levels of both cholesterol and triglycerides were independently associated with regression of microalbuminuria. Moreover, these factors had additive effects on regression of microalbuminuria.

A small number of studies reported an association between dyslipidemia and loss of renal functions. Regarding the rate of decline in glomerular filtration rate (GFR), a prospective study of 30 patients with type 1 diabetes revealed that high serum cholesterol, triglycerides and apolipoprotein B were correlated to a rapid decline in glomerular filtration rate [27].

As described above, evidence has been accumulated to suggest that dyslipidemia is one of the risk factors for progression and regression of diabetic nephropathy. However, as far as we knew, there have been few studies reporting the association with end-stage renal disease, or renal replacement therapy. A report of a scientific workshop sponsored by the National Kidney Foundation (NKF) and the US Food and Drug Administration (FDA) indicated that evidence was insufficient to use a change of albuminuria as a surrogate marker as a clinical endpoint [28].

Long-term follow-up studies are needed to demonstrate the causal relationships between dyslipidemia and end-stage renal disease from diabetic nephropathy.

Treatment of dyslipidemia and diabetic nephropathy

With regard to the treatment of dyslipidemia in patients with diabetes, there were some interventional trials of anti-hypercholesterolemic agents including fibrates and statins.

The Diabetes Atherosclerosis Intervention Study (DAIS) is a randomized study that assessed the effect of fenofibrate on type 2 diabetic patients [29]. In this study, fenofibrate reduced the worsening of urine albumin excretion and the effects were mainly observed in the progression from normoalbuminuria to microalbuminuria. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study also evaluated the effect of fenofibrate on type 2 diabetes [30]. From this study, it was proved that fenofibrate is effective in lowering the decline of the estimated glomerular filtration rate (eGFR) and reducing the progression of albuminuria. Additionally in this study, patients treated with fenofibrate had higher rates of regression of albuminuria than the placebo group. This evidence suggests that fenofibrate is effective in ameliorating diabetic nephropathy. In a meta-analysis of these two studies, the significant effect on the regression from microalbuminuria to normoalbuminuria was proved; however, progression from microalbuminuria to macroalbuminuria was not significant [31].

The effect of statins on diabetic nephropathy was examined in the Collaborative Atorvastatin Diabetes Study (CARDS) [32]. Treatment with atorvastatin was compared with a placebo in this study, and was associated with an improvement in annual changes in eGFR (0.18 mL/min/1.73 m^2/year). It is noteworthy that atorvastatin ameliorated eGFR without improving albuminuria, when comparing angiotensin-converting enzyme inhibitors which have renoprotective effects and prevent the onset of albuminuria [33].

There is still a lot of uncertainty about the effect of statins. The effect on renal protection was not demonstrated in the Study of Heart and Renal Protection (SHARP) which included 2,094 (33 %) patients with diabetes [34], and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) which included 3,638 (36 %) patients with diabetes [35]. A meta-analysis also showed that regression of albuminuria [31] and changes in eGFR [36] were not observed in patients with diabetes treated with statins.

There seems to be no definite answer for treatment of dyslipidemia in diabetic patients from the viewpoint of anti-hyperlipidemic agents. One of the supposed causes of inconsistency in results is that kidney diseases in patients with diabetes may not be uniform, but consist of many renal diseases [37]. In some cases, renal biopsies might be needed to assess the accurate risks [38].

Diabetic patients are at higher risk for cardiovascular mortality compared with non-diabetic patients [10, 39]. There is sufficient evidence, such as SHARP [34], to show that statins reduce the risk of cardiovascular events. Considering these facts, many diabetic patients might benefit from statin treatment. An increasing number of patients are now receiving this treatment. In the analysis of the National Health and Nutrition Examination Survey (NHANES) 2005–2006, 93.5 % of diabetic men aged 65–69 without cardiovascular disease received statins [40].

On the other hand, administration of statin may have adverse side-effects, including myopathy [41], renal toxicity [42], and incident diabetes [43]. A study comparing the risks and benefits of statins concluded that cardiovascular benefits outweigh the increased risk of new-onset diabetes [44]. It is beyond doubt that each patient's risk must be taken into account before administration of statins.

It is also important to consider changes in life-style; however, the difficulty lies in improving renal and cardiovascular events through life-style changes [45]. It remains a challenge for future research to examine the impact of life-style changes.

Concluding remarks and future directions

In considering the complexity of the problem of diabetic nephropathy, many aspects of a patient's condition and treatment should be taken into account. Further insight into the pathogenesis of dyslipidemia, and the risk and benefits of each treatment may be beneficial for each patient.

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Conflict of interest The authors have declared that no conflict of interest exists.

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