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Role of lipid control in diabetic nephropathy

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Role of lipid control in diabetic nephropathy. Patients with diabetic nephropathy are known to be associated with many lipoprotein abnormalities, including higher plasma levels of very low-density lipoprotein, low-density lipoprotein and triglycerides, and lower levels of high-density lipoprotein. Many studies have reported that lipids may induce both glomerular and tubulointerstitial injury through mediators such as cytokines, reactive oxygen species, chemokines, and through hemodynamic changes. Clinical studies in patients with diabetic nephropathy showed that lipid control can be associated with an additional effect of reduction in proteinuria. Experimental studies demonstrated that lipid-lowering agents exerted a certain degree of renoprotection, through both indirect effects from lipid lowering and a direct effect on cell protection. Therefore, lipid control appears to be important in the prevention and treatment of diabetic nephropathy.

Diabetic nephropathy has become the leading cause of end-stage renal failure in many countries, including Taiwan. One of the major risk factors for the development and progression of diabetic nephropathy is dyslipidemia. In this paper we will review the role of lipid in mediating renal injury and the beneficial effects of lipid control in diabetic nephropathy.

LIPOPROTEIN ABNORMALITIES IN DIABETIC NEPHROPATHY

Patients with diabetic nephropathy often have multiple lipoprotein abnormalities [1]. In patients with microalbuminuria and overt proteinuria, increased plasma levels of very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and triglycerides are usually found. However, the plasma level of high-density lipoprotein (HDL) is lower than those patients with normoalbuminuria. In addition to the abnormalities in amount of lipoprotein, the diameter of LDL particles is also reported to be smaller in patients with diabetic nephropathy [2, 3] compared to diabetic patients without nephropathy. All the lipoprotein abnormalities mentioned above become more severe with declining renal function and increasing albuminuria. In those diabetic patients with nephrotic syndrome and advanced renal failure, the patterns of dyslipoproteinemia are not different from those patients without diabetes.

Recent studies also suggest that apolipoprotein (apo) E gene polymorphism may be important in the development of diabetic nephropathy [4, 5]. Although results are still conflicting, our study in Taiwanese patients demonstrated that the frequency of apo E2 allele was significantly higher in patients with diabetic nephropathy than in normal controls and diabetics without nephropathy [6]. These findings imply that apo E polymorphism is apparently related to the development of diabetic nephropathy in type 2 diabetes in Taiwan.

LIPID-INDUCED RENAL INJURY IN DIABETIC NEPHROPATHY

Dietary-induced hypercholesterolemia in animals induced focal glomerulosclerosis [7], and lipid-lowering treatment in Zucker rats was associated with attenuation in glomerular lesions [8]. Animal studies also demonstrated a damaging effect of hyperlipidemia on the tubulointerstitium [9], which is also a major feature of diabetic nephropathy and an important predictor of renal dysfunction [10]. Recent study demonstrating that hyperlipidemia and hyperglycemia act synergistically to induce renal injury in LDL receptor-deficient mice [11] has further indicated that lipid can exacerbate diabetic nephropathy. Dyslipidemia may also cause or exacerbate diabetic nephropathy by alterations in the coagulation-fibrinolytic system, changes in membrane permeability, damage to endothelial cells, and increased atherosclerosis [12].

Clinical study on the correlation between hyperlipidemia and renal dysfunction in patients with diabetic nephropathy is difficult due to the complex interrelation between serum lipid, blood glucose, and proteinuria. In a study on 53 normoalbuminuric type 1 diabetic patients, Watts et al found that the development of microalbuminuria after 10 years' follow-up was closely related to baseline serum cholesterol and LDL cholesterol levels [13]. Parving et al also found a close relationship between serum cholesterol level and the progression of renal dysfunction in a 10-year prospective study in type 1

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diabetic patients with nephropathy [14]. In studies on patients with type 2 diabetes, baseline level of serum cholesterol was also found to be the independent risk factor for the development of diabetic nephropathy [15, 16]. However, conflicting results were found between the effects of serum lipid on the progression of renal function in type 2 diabetes [17, 18].

The mechanisms by which lipid induced renal injury are not clear. We have demonstrated that both native and oxidized LDL enhance superoxide production from freshly isolated diabetic rat glomeruli [19], and the reactive oxygen species enhances endothelin-1 production of diabetic rat glomeruli in vitro and in vivo [20]. Other factors, such as transforming growth factor-β1 (TGF-β1), were also suggested to be an important mediator in lipid-induced renal injury in diabetic nephropathy [21].

CLINICAL EFFECTS OF LIPID CONTROL IN DIABETIC NEPHROPATHY

Although lipid-lowering treatment has been shown to be effective in reducing cardiovascular morbidity and mortality in diabetic patients with hyperlipidemia, their effects on diabetic nephropathy are still unclear due to lack of prospective randomized intervention studies. Early studies have demonstrated that treatment with the HMG CoA reductase inhibitor pravastatin decreases albuminuria in patients with type 2 diabetes [22, 23]. However, later studies showed either beneficial or no effects on albuminuria with HMG CoA reductase inhibitors in both type 1 or type 2 patients [24–27]. In general, these studies involved only a small number of patients, and the duration of follow-up was short, making it inadequate in assessing the clinical effects of lipid control in diabetic nephropathy.

EXPERIMENTAL STUDIES ON THE EFFECT OF LIPID CONTROL IN DIABETIC NEPHROPATHY

Diabetic glomerulosclerosis is characterized by an increase in mesangial matrix, and the close resemblance on the pathogenesis of glomerulosclerosis to atherosclerosis has led to the speculation that lipids are involved in the development of diabetic nephropathy. We have demonstrated that pravastatin suppresses the effects of high glucose on the proliferation and the production of superoxide and fibronectin of mesangial cells [28]. Since both the proliferation and the increased superoxide production of mesangial cells occur early during the progress of diabetic nephropathy [29], early treatment with pravastatin might postpone the progression of glomerular injury in patients with diabetic nephropathy. Transforming growth factor-β (TGF-β) may be an important mediator involved because high glucose causes an increase in expression of TGF-β in the glomeruli of streptozotocin-diabetic rats [30], and pravastatin suppresses the activity of TGF-β induced by high glucose [31]. Another study also demonstrated that simvastatin prevents high glucose-induced proliferation of mesangial cells via modulation of Rho GTAase/p21 signaling pathway [32], which provides a molecular basis for the use of statins in early stages of diabetic nephropathy.

We have also demonstrated that pravastatin suppresses the effect of both LDL and oxidized-LDL on mesangial cells [28, 33], which is important because an increased plasma level of oxidized-LDL has been found in diabetic patients [34], especially in those patients with macroalbuminuria [35]. Our previous study has demonstrated that the oxidative stress and the oxidative modification of LDL can be effectively inhibited by insulin [36], suggesting that insulin may have an additional effect to prevent the generation of atherogenic lipoproteins in vivo. There is accumulating evidence that statins have beneficial effects that are independent of the classic actions on lipid lowering [37]. These effects include: improving endothelial function, reducing LDL oxidation, reducing platelet aggregability, reducing procoagulation factors, and inhibiting smooth muscle cell proliferation.

The mechanisms by which HMG-CoA reductase inhibitors reduce renal lesions remain unclear. Recent studies have suggested that metabolites of the mevalonate pathway play a critical role in cell proliferation [38, 39]. Mevalonate is synthesized intracellularly from HMG-CoA by the actions of HMG-CoA reductase [40]. Thus, it is thought that inhibition of HMG-CoA reductase by pravastatin leads to loss or significant reduction of mevalonate, subsequently inhibiting DNA synthesis as well as cell proliferation in several types of cells, including mesangial cells. Since the inhibition of pravastatin on the macrophage growth induced by oxidized-LDL is reversed by the addition of mevalonate [41], its role in cell proliferation is further implicated. Weiss et al have also shown that short-term (1 hour) incubation of pravastatin induces apoptosis of vascular smooth muscle cells [42], an effect that may also be involved in the depletion of cell numbers in diabetic glomerulosclerosis.

CONCLUSION

Dyslipidemia is common in diabetic patients. Many clinical and experimental studies suggest that serum cholesterol may play important role in the development and progression of diabetic nephropathy. Although large-scaled prospective, randomized, controlled studies are still lacking, lipid control appears to be important in the prevention and treatment of diabetic nephropathy.

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