

POTENTIAL INFLUENCE OF LIPIDS IN DIABETIC NEPHROPATHY: INSIGHTS FROM EXPERIMENTAL DATA AND CLINICAL STUDIES

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SUMMARY - Diabetic nephropathy is associated with an altered lipid profile characterized by elevated triglyceride rich lipoproteins, present even in the earlier stages of the renal disease. Although many experimental studies have demonstrated a significant deleterious role for hyperlipidemia in both the initiation and progression of renal injury, data remain more conflicting in humans. A few prospective studies, mostly in type 2 diabetes, have suggested an independent role for serum cholesterol level in the subsequent development of incipient or overt diabetic nephropathy. Furthermore, studies have reported in both types of diabetes an independent deleterious influence of serum total cholesterol on the decline in renal function and/or progression of albuminuria. However, the majority of these studies were post hoc analyses of previously controlled therapeutic trials with several observational studies not confirming these findings. It remains controversial whether apolipoprotein E gene polymorphism is an important factor in the development of diabetic nephropathy. Most of the interventional studies with lipid-lowering therapy in diabetic nephropathy have used HMG CoA reductase inhibitors and have been inconclusive. This may be due to a too short follow-up or insufficient number of patients. Further larger prospective studies are therefore required to better ascertain the role of lipids in the progression of diabetic nephropathy.

Key-words: diabetic nephropathy, lipoproteins, lipids, albuminuria, angiotensin II.

RÉSUMÉ - Rôle potentiel des lipides dans la néphropathie diabétique : des données expérimentales aux études cliniques.

La néphropathie diabétique est associée à des altérations lipidiques caractérisées par une élévation des lipoprotéines enrichies en triglycérides qui est observée dès les premiers stades de l'atteinte rénale. Bien que de nombreuses études expérimentales aient montré que des altérations du métabolisme lipidique pouvaient être associées à la formation et à la progression des lésions rénales, les données chez l'homme sont plus contradictoires. Quelques études prospectives, la plupart dans le diabète de type 2, ont suggéré un rôle prédictif indépendant de la cholestérolémie pour le développement ultérieur d'une néphropathie. D'autres études ont montré que la cholestérolémie était un facteur de risque indépendant du déclin de la fonction rénale et/ou de la progression de l'albuminurie. Cependant, la plupart de ces études étaient des analyses post hoc d'essais antérieurs et certaines études d'observation n'ont pu confirmer ces résultats. Les données concernant l'influence du polymorphisme du gène de l'apo E sur le développement de la néphropathie diabétique demeurent controversées. La majorité des études d'intervention évaluant les effets des hypolipémiants ont utilisé les inhibiteurs de l'HMG CoA réductase et ont obtenu des résultats non concluants, en raison d'un effectif trop faible et d'un suivi trop restreint. De plus larges études prospectives sont ainsi nécessaires afin de confirmer l'influence du cholestérol dans la néphropathie diabétique.

Mots-clés : néphropathie diabétique, lipoprotéines, lipides, albuminurie, angiotensine II.

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It is already about fifty years since Wilens and Elster raised the hypothesis that hyperlipidemia may contribute to renal disease in diabetes [1]. Since then, many experimental studies have described the presence of renal lesions associated with abnormal lipid metabolism with investigations suggesting an influence of dyslipidemia on the formation of glomerular lesions, especially focal glomerular sclerosis [2-6]. In the early 80's, it was formally proposed that dyslipidemia may promote the progression of chronic renal disease [7, 8]. But it was only over the past decade that clinical studies have attempted to assess the role of lipids in the progression of diabetic nephropathy, in both type I and type II diabetes [9, 10, 11]. This paper reviews the available evidence for a possible linkage between serum lipid levels, apolipoprotein E genotype and both the development and the clinical course of diabetic nephropathy.

■ LIPOPROTEINS ABNORMALITIES IN DIABETIC NEPHROPATHY

In both type I and type II diabetes, various abnormalities in plasma concentrations of lipoproteins have been reported to be present in diabetic nephropathy, even in the earlier stages of the renal disease [12-18].

Incipient and overt clinical diabetic nephropathy

In comparison to normoalbuminuric diabetic patients, those with microalbuminuria and overt pro-

teinuria have been reported to have significantly higher plasma concentrations of very low density lipoprotein (VLDL), low density lipoprotein (LDL) and triglyceride but lower levels of high density lipoprotein cholesterol (HDL) [12-18]. No major compositional changes in lipoproteins have been observed between patients with microalbuminuria and albuminuria [17]. Elevated plasma concentrations of apolipoprotein B, apoC-III and apoprotein(a), and increased mass concentrations of the highly atherogenic intermediate-density lipoprotein fraction (IDL) have also been reported in patients with both microalbuminuria and albuminuria in comparison to normoalbuminuric diabetic subjects [12-18].

Furthermore, the diameter of LDL particles, which is strongly regulated by plasma triglyceride level, has been reported to be smaller in patients with diabetic nephropathy, including those with microalbuminuria, as compared to diabetic patients without nephropathy [19]. The postprandial lipemia has been shown to be significantly greater in diabetic patients with nephropathy when compared with normoalbuminuric patients, suggesting that the reduction of LDL particle size in diabetic nephropathy is closely related to early modification of triglyceride-rich lipoproteins metabolism [14, 19].

An increase in hepatic lipase (HL) activity and a reduced postheparin plasma lipoprotein lipase (LPL)/HL ratio have been reported in micro and macroalbuminuric patients as compared with normoalbuminuric diabetic subjects [16, 17].

All these multiple lipoprotein abnormalities described in diabetic patients with nephropathy become more accentuated with decreasing renal function and increasing urinary albumin excretion [7, 12, 18].

ABBREVIATIONS

- ACE:** Angiotensin converting enzyme
- Apo B:** Apolipoprotein B
- Apo C-II:** Apolipoprotein C-II
- Apo C-III:** Apolipoprotein C-III
- Apo E:** Apolipoprotein E
- CRF:** Chronic renal failure
- HDL:** High-density lipoprotein
- HL:** Hepatic lipase
- HMG-CoA:** 3-hydroxy-3-methylglutaryl coenzyme A
- ICAM-1:** Intercellular adhesion molecule-1
- IDL:** Intermediate-density lipoprotein
- LDL:** Low-density lipoprotein
- Lp(a):** Lipoprotein(a)
- LPL:** Lipoprotein lipase
- MCP-1:** Monocyte chemoattractant protein-1
- M-CSF:** Monocyte colony-stimulating factor
- PDGF:** Platelet-derived growth factor
- RAS:** Renin angiotensin system
- TGFβ:** Transforming growth factor β
- VCAM-1:** Vascular cell adhesion molecule-1

Nephrotic syndrome

Diabetic patients with nephrotic syndrome often have altered lipoprotein concentrations and composition. Increased triglyceride-rich lipoproteins, VLDL, chylomicrons and remnant particles but also elevated LDL and Lp(a) concentrations have been reported in these patients [20, 21]. These lipoprotein abnormalities become more severe when chronic renal failure is associated with nephrotic syndrome. However, it has been shown that diabetes mellitus does not significantly affect the pattern of hyperlipoproteinemia of nephrotic syndrome compared to non-diabetic subjects [21].

Diabetic renal failure and chronic hemodialysis treatment

Diabetic renal failure shares the same characteristic profile of the dyslipoproteinemia of chronic renal failure (CRF) with accumulation of triglyceride-rich apoB-containing lipoproteins, reduced levels of

apoAI, apoA-II, elevated levels of apoB, decreased apoC-II/apoC-III ratio and reduced LPL activities in plasma [22, 23]. But, when compared to non diabetic CRF patients, these lipid abnormalities are more marked in diabetic nephropathy probably reflecting the additional impact of the diabetic state and in particular the level of metabolic control [22].

Diabetic patients receiving continuous hemodialysis treatment exhibit typically hypertriglyceridemia and elevated serum apo B associated with a marked reduction in HDL cholesterol and apo A-1 levels [24]. Elevated Lp(a) concentration is also observed at this stage, as described in non-diabetic hemodialysis patients. Serum total cholesterol and LDL-cholesterol levels are only slightly elevated [25].

Triglyceride enrichment of VLDL and LDL appears to be a consistent feature of diabetic hemodialysis patients, which is less pronounced in non-diabetic patients [25]. The apo B/apo A-1 ratio has also been reported to be significantly higher in diabetic patients than in non-diabetic subjects undergoing continuous hemodialysis [24], emphasizing the diabetes-related lipid abnormalities in end-stage renal failure.

■ POTENTIAL INFLUENCE OF LIPIDS IN THE PATHOGENESIS OF DIABETIC NEPHROPATHY

Experimental studies

Previous experimental studies have reported a link between hyperlipidemia and the formation of glomerulosclerosis. Dietary induced hypercholesterolemia in rats, guinea pigs and rabbits was associated with a premature development of focal glomerulosclerosis [2-5]. Experiments in the obese Zucker rat which represents a model of dyslipidemia with peripheral insulin resistance, showed that hyperlipidemia may induce glomerular injury, especially focal glomerular sclerosis, independently of glomerular hemodynamics [26, 27]. Furthermore lipid-lowering treatment has been shown to attenuate renal lesions in Zucker rats and in the subtotal nephrectomy model, emphasizing a possible pivotal role for lipids in the pathogenesis of progressive renal disease [26, 27]. The influence of hyperlipidemia on renal function may be even more important in the presence of other risk factors like arterial hypertension, renal ablation or diabetes mellitus [3, 26]. The mechanisms by which lipids cause or exacerbate glomerular injury remain incompletely understood.

Mechanisms of lipid-induced renal injury

In the glomerulus

In human glomeruli, both mesangial and epithelial cells take up lipoproteins via specific receptors [28,

29]. Mesangial cells also express scavenger receptors which are involved in the preferential uptake of modified, glycosylated and oxidized LDL, as observed in diabetes [30]. Accumulation of modified LDL in the mesangium or in mesangial matrix has been reported to favor their uptake by infiltrated glomerular monocytes, leading in turn to the subsequent activation of these cells into macrophages [31, 32]. This preferential phagocytosis of modified LDL by monocytes has been also reported to play a pivotal role in the formation of mesangial foam cells [33]. As outlined in *Figure 1*, accumulated mesangial modified lipoproteins may influence the pathogenesis of glomerulosclerosis by different mechanisms: Exposure to oxidized lipoproteins has been reported to stimulate mesangial cell secretion of various chemotactic factors and adhesion molecules (M-CSF, ICAM-1, VCAM-1), enhancing the renal recruitment of macrophages [34]. These factors result in monocyte infiltration which has been reported to play a key role in the pathogenesis of glomerulosclerosis and tubular fibrosis, in particular in diabetic nephropathy [35]. These intramesangial recruited macrophages may in turn further oxidize LDL, creating a vicious self-perpetuating cycle resulting in progressive renal injury (*Fig. 1*). Renal activated macrophages have been shown to stimulate the release of reactive oxygen species and the expression of pro-sclerotic and proliferative cytokines such as transforming growth factor $\beta 1$ (TGF- $\beta 1$) and platelet-derived growth factor-AB (PDGF-AB). These cytokines stimulate the production of extra-cellular matrix proteins, promoting mesangial expansion as has been described in diabetic nephropathy [36]. In vitro studies have demonstrated that LDL and oxidized LDL stimulate TGF- $\beta 1$ gene expression in both human glomerular mesangial and epithelial cells [37, 38].

Therefore, TGF- $\beta 1$ appears to be an important mediator of lipid-induced mesangial matrix expansion as well as playing a key role in the pathogenesis of diabetic nephropathy [31, 37, 38, 39]. Finally, the uptake of modified LDL by macrophages has been reported to stimulate eicosanoid synthesis including thromboxanes and leukotrienes, leading to potentially deleterious alterations in intra-glomerular hemodynamics [33]. In this regard, dietary cholesterol supplementation in animals has been shown to result in an increase in efferent arteriole resistance and a subsequent elevation in intra-glomerular pressure [40]. This effect may exacerbate glomerular injury in diabetic nephropathy (*Fig. 1*). However, one must be cautious in extrapolating the findings of these studies to human diabetic nephropathy since most of the *in vivo* studies reported above were conducted in non diabetic models of renal disease, with a focus on focal glomerulosclerosis. Indeed, it has been reported that dietary cholesterol supplementation in Sprague Dawley rats with streptozotocin-induced diabetes did not influence uri-

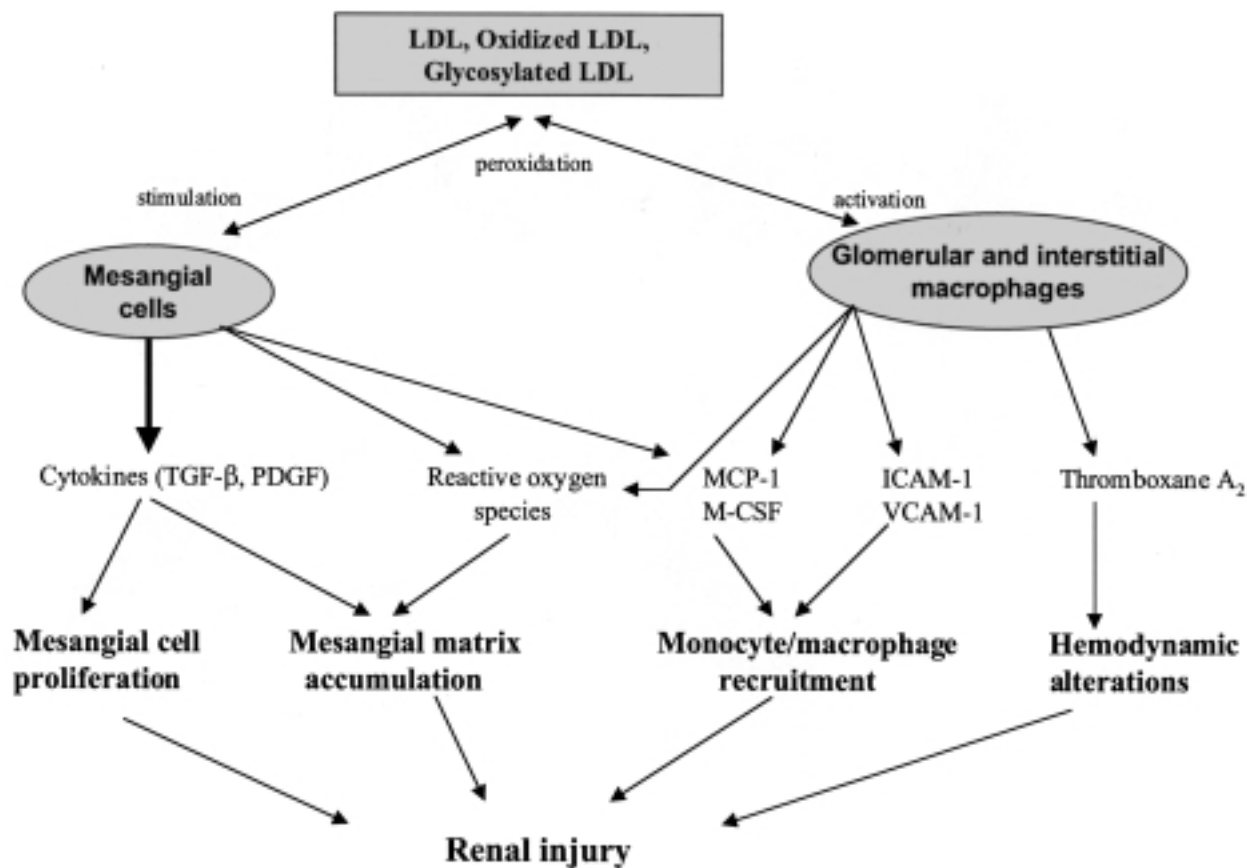


FIG. 1. Schematic representation of possible pathophysiological mechanisms mediating lipid-induced renal injury.

nary albumin excretion and any glomerular ultrastructural parameter [41]. Nevertheless, the data from these experimental studies in different models may be relevant, at least in part, for the pathogenesis of lipid-induced renal injury in diabetic nephropathy.

In the tubulointerstitium

Tubulointerstitial injury has been clearly demonstrated over the last decade to play a pivotal role in the pathogenesis of diabetic nephropathy and to be an important predictor of renal dysfunction [35]. Animal studies have demonstrated a damaging effect of hyperlipidemia on the tubulointerstitium [42]. Although it had been reported in hyperlipidemic Zucker rats that tubulointerstitial injury closely paralleled the development of glomerulosclerosis [5], other authors have described that lipid-induced tubulointerstitial lesions may precede glomerular changes or occur independently of the glomerular lesions [42]. In these experimental studies, hyperlipidemia-induced chronic tubulointerstitial damage was associated with significant interstitial macrophage infiltration and a parallel increase in TGF- β 1 gene expression in interstitial cells,

suggesting a cytokine-mediated role for lipids in the development or aggravation of tubulointerstitial lesions [34, 42]. Furthermore, in proteinuric conditions such as overt diabetic nephropathy, it has been proposed from experimental *in vivo* studies that the tubular uptake and metabolism of the lipid component of filtered lipoproteins lead to local expression of chemokines and cytokines and promote interstitial inflammation [43].

Potential interactions between angiotensin II and the lipid nephrotoxicity in diabetic nephropathy

There is evidence suggesting activation of the renin-angiotensin system (RAS) in the kidney in diabetes [44]. In particular, the major effector peptide of this pathway, angiotensin II, is viewed to play a pivotal role in the pathogenesis of diabetic nephropathy [36]. There may be an interplay of lipoproteins and angiotensin II-induced renal injury pathways in diabetic nephropathy. As summarized in *Figure 2*, some of the pathophysiological mechanisms of lipid induced nephrotoxicity are also observed with angiotensin II-induced renal disease. Firstly, angiotensin II

has been showed to increase oxidant stress, and this would favor the formation of oxidized LDL which plays a key role in the formation of renal lesions. Secondly, angiotensin II increases microvascular glomerular permeability and may therefore enhance glomerular macromolecules traffic and lead to both mesangium lipid accumulation and tubular lipoprotein overload. Lastly, it has been demonstrated that angiotensin II stimulates gene expression of many cytokines and chemokines, potentially enhancing lipid-induced macrophage infiltration, extracellular matrix accumulation and promoting the subsequent formation of renal injury (Fig. 2). Furthermore, experimental studies have showed that ACE inhibitors may reduce lipid-induced glomerular lesions in obese diabetic rats [45]. These experimental findings are consistent with clinical data which have suggested that in diabetic nephropathy, the specific deleterious influence of serum cholesterol was markedly attenuated by ACE inhibitor treatment [9, 11]. Mulec *et al.* found that in type 1 diabetic patients, the ACE inhibitor treatment, in contrast to the beta blocker metoprolol, was associated with a marked reduction in the decline of renal function over 2.5 years [9]. This renoprotective effect was

also observed in the subgroup of patients with baseline hypercholesterolemia. ACE inhibitor treatment and serum cholesterol levels were two mutually independent risk factors for the subsequent decline in renal function [9]. These data suggest additive effects of these two parameters on loss of renal function.

Furthermore, a reduction in cholesterol secondary to the antiproteinuric effect of ACE inhibitor could further enhance the beneficial renal effects of these agents [46].

■ ROLE OF LIPIDS IN THE DEVELOPMENT OF DIABETIC NEPHROPATHY

Only a few studies have prospectively assessed the potential influence of initial serum lipid levels on the subsequent development of incipient or overt diabetic nephropathy. The close interrelationships between serum lipids values, blood glucose status and proteinuria make more difficult to determine the influence of lipids per se in the progression of diabetic nephropathy, particularly in uncontrolled observational studies.

In type 1 diabetes

Watts *et al.* reported in 53 normoalbuminuric type 1 diabetic patients that the increase in albuminuria after 10 years follow-up was significantly and positively related to the baseline serum total cholesterol, LDL cholesterol and apolipoprotein B levels [47]. In that study, no significant association was found with triglycerides, HDL cholesterol, apo A-I and Lp(a) levels. Among the variables entered in a multivariate statistical analysis, only initial serum apo B level was an independent predictor of the progression of very low-level albuminuria [47]. However, only 5 patients progressed to microalbuminuria, potentially limiting the relevance of these findings.

In type 2 diabetes

In a prospective observational study with a mean 5.8 years follow-up, Gall *et al.* from the Steno Diabetes Center have evaluated the main risk factors for the development of persistent micro and macroalbuminuria in 191 normoalbuminuric type 2 diabetic patients. They found in a multivariate analysis that baseline concentration of serum cholesterol, but not HDL cholesterol, was an independent risk factor for the development of incipient or overt diabetic nephropathy [48]. The potential influence of serum triglycerides was not evaluated in that study. That study agrees with findings observed in Pima Indians, in whom serum cholesterol level was found to be related to the development of increased urinary albumin excretion [49]. More recently, Ravid *et al.* provided further evidence

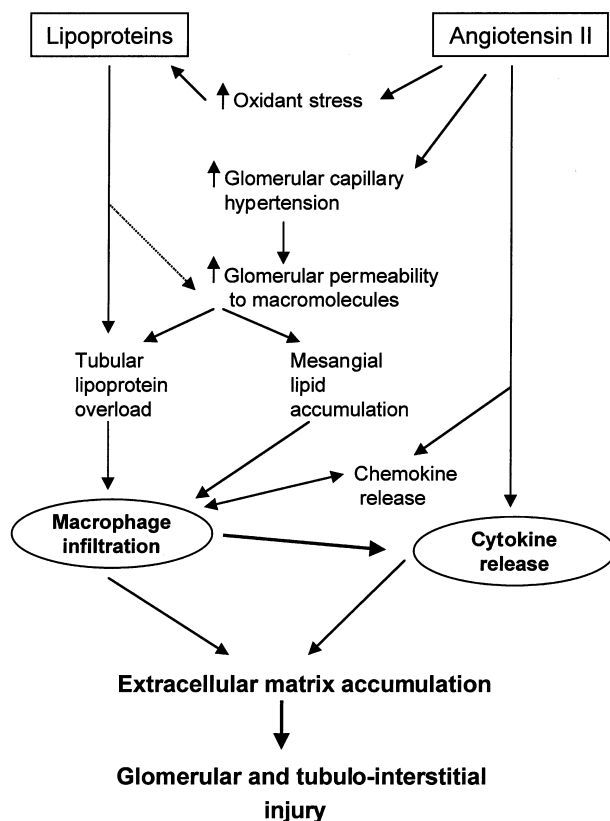


FIG. 2. Potential interactions between lipoproteins and angiotensin II in the pathogenesis of diabetic nephropathy.

for an independent role of plasma cholesterol in the subsequent loss of renal function and increase in urinary albumin excretion in diabetic subjects without nephropathy [50]. In an uncontrolled prospective study, 574 patients, initially normotensive with both normal renal function and urinary albumin excretion rate were followed-up for a mean period of 7.8 years. In a multiple logistic regression analysis, baseline serum total cholesterol level, mean blood pressure and glycosylated hemoglobin were the main independent determinants of the subsequent decline in renal function (assessed as the reciprocal creatinine value). The risk to develop microalbuminuria was also independently predicted by the baseline values of total cholesterol, mean blood pressure, glycosylated hemoglobin, HDL cholesterol and the body mass index [50].

■ ROLE OF LIPIDS IN THE PROGRESSION OF DIABETIC NEPHROPATHY

In both type I and type II diabetes, only a few prospective and case-control studies have attempted to establish a correlation between hyperlipidemia and the decline of renal function in diabetic nephropathy. However most of these studies were post-hoc secondary analyses of previous controlled trial assessing the renal effects of angiotensin converting enzyme (ACE) inhibitors in diabetic nephropathy.

In type I diabetes

Mulec *et al.* prospectively studied over 2.5 years the relationship between serum lipid values and the subsequent decline in glomerular filtration rate (GFR) in 30 type I diabetic patients with already advanced renal disease and proteinuria at the time of commencement of the study [9]. All patients were on antihypertensive treatment with either enalapril or metoprolol. These investigators demonstrated that the decline in GFR was negatively correlated to initial values of plasma total cholesterol, triglycerides and apolipoprotein B and was positively correlated to Apo AI [9]. There was no correlation between Lp(a) level and the decline in renal function. In a stepwise regression analysis taken into account multiple covariates, including glycosylated hemoglobin, arterial blood pressure and albuminuria, the strongest factors linked to decline in GFR were serum cholesterol and the type of antihypertensive treatment.

Parving *et al.* found a significant positive correlation in univariate analysis between serum cholesterol level and the rate of decline in GFR in a 10 year prospective study of ACE inhibitors in diabetic nephropathy [51]. These patients were all hypertensive with persistent albuminuria without evidence of chronic renal failure. However this association with

serum cholesterol levels did not remain significant after a stepwise multiple regression analysis which included other variables such as mean arterial blood pressure, albuminuria and glycemic control.

Krolewski *et al.*, in a post-hoc analysis of the data collected during the prospective Diabetic Retinopathy Study, examined the determinants of progression to chronic renal failure (assessed by serum creatinine) in 439 patients with diabetic nephropathy. All these patients had severe diabetic retinopathy and either intermittent or persistent proteinuria and were followed-up for more than 3 years [10]. Only one third of the patients experienced a rapid loss of renal function. Among the different baseline variables analyzed, only serum cholesterol level and diastolic blood pressure at entry were significantly associated with a rapid loss of renal function. These correlations remained significant in a multiple logistic regression analysis.

In type II diabetes

Ravid *et al.* have followed prospectively for five years 94 normotensive patients with microalbuminuria and normal renal function. These patients were randomized to receive either enalapril or placebo [11]. These authors reported a significant correlation between baseline and mean study values of serum total cholesterol and the subsequent evolution of renal function (expressed as the ratio of initial to final reciprocal serum creatinine values). This association persisted after stratification for blood pressure and was observed in both the enalapril and placebo treated groups. In the placebo as well as in enalapril treated patients, initial and mean plasma total cholesterol and mean blood pressure were also significant predictors of the subsequent increase in albuminuria [11]. No correlation was found in that study between serum HDL cholesterol or triglyceride levels and either the renal outcome or the increase in albuminuria. However, other investigators have reported in type 2 diabetes a significant independent influence of the serum triglyceride level on progression of microalbuminuria [52] and progressive loss of renal function in diabetic nephropathy [53]. Furthermore, in these studies, serum cholesterol did not emerge as a significant predictor of renal outcome. Lastly, it should be noted that a number of other observational studies have failed to demonstrate any independent effect of any serum lipid parameter on either evolution of albuminuria or the decline in renal function [54, 55, 56].

■ INFLUENCE OF APOLIPOPROTEIN E GENE POLYMORPHISM IN DIABETIC NEPHROPATHY

Apolipoprotein E is a major constituent of lipoproteins involving in the uptake and clearance of lipopro-

teins. A triallelic polymorphism of apo E gene resulting in three isoproteins ($\epsilon 2$, $\epsilon 3$ and $\epsilon 4$ alleles) has been reported to have an influence on lipids levels and to be associated with the development of vascular disease [57].

Recent studies have assessed the role of the apo E gene polymorphism in the development of diabetic nephropathy, with conflicting findings.

In type 1 diabetes, a large study including 719 Caucasian patients found a significant association between the presence of $\epsilon 2$ allele and diabetic nephropathy [58].

Similarly, Werle *et al.* found that the $\epsilon 2$ allele was a significant predictor of the mean albumin excretion rate in a stepwise multiple regression analysis involving 162 type 1 diabetic patients with various stages of diabetic nephropathy [59]. Although carriers of the $\epsilon 2$ allele also had a lower GFR than $\epsilon 2$ allele non carriers, no significant association between the stage of nephropathy and the apo E genotype was observed in that study. These findings have some similarities to those reported by Onuma *et al.* from the Joslin Diabetes Center who showed no significant association between apo E genotypes or allele frequencies and the development of either incipient or overt diabetic nephropathy in 146 type 1 diabetic patients [60]. Similarly, Hadjadj *et al.* did not observe any significant association between apo E gene allelic frequencies and the development of diabetic nephropathy in a large cohort of 494 French type 1 diabetic patients with proliferative retinopathy [61].

Data in type 2 diabetes are also conflicting as has been observed in the studies in type 1 diabetes. Differences in results may probably relate to ethnicity. An excess of the $\epsilon 2$ allele has been reported in 146 Japanese patients with diabetic nephropathy when compared to normoalbuminuric subjects [62]. In addition, the $\epsilon 4$ allele which is associated with a higher plasma cholesterol level has been described as an independent protective factor for the progression to end stage renal disease in 178 Japanese type 2 diabetic patients [63]. By contrast, Boizel *et al.* reported that French subjects carriers of the $\epsilon 2$ allele had less albuminuria and a significantly reduced prevalence of diabetic nephropathy when compared to other allele carriers [64].

■ INTERVENTION STUDIES WITH LIPID-LOWERING THERAPY IN DIABETIC NEPHROPATHY

Experimental models

Although lipid-lowering agents have been described in different animal models of renal disease to exert a degree of renoprotection [26, 27], their role in experimental diabetes remains unclear. Indeed, most of the studies which have assessed the renal effects of lipid-lowering agents in experimental diabetic models

have evaluated HMG CoA reductase inhibitors and it remains difficult to determine whether the potential renal effect of these agents was directly related to lipid lowering or to other specific biological properties of this class of drugs.

It has been then described in streptozotocin-induced diabetic rats that lovastatin 8 weeks-treatment was associated with a significant preservation of GFR, in comparison to diabetic control animals [65]. This renoprotective effect of the evaluated HMG CoA reductase inhibitor was similar to that conferred by an ACE inhibitor and was associated with a significant reduction in mesangial histological lesions. However, the renoprotective effects of lovastatin appeared to be independent of plasma lipid levels changes [65]. Similarly, Kim *et al.* have very recently reported in this same diabetic rat model that lovastatin 12 months treatment suppressed the increase in albuminuria, kidney weight, glomerular volume despite chronic hyperglycemia [61]. The investigators demonstrated that lovastatin blunted the increase in glomerular TGF β 1 gene expression observed in untreated diabetic rats. The investigators suggested that this direct cellular effect of lovastatin may at least in part explain why this drug was observed to delay the onset and progression of diabetic nephropathy in this experimental model [66].

These results are consistent with those reported in experimental models of non-diabetic renal disease in which HMG CoA reductase inhibitors have been described to reduce albuminuria excretion and to attenuate the development of glomerulosclerosis [67, 68, 69]. As in some of these studies, HMG CoA reductase inhibitors had no significant effect on plasma lipid levels, the reported renoprotective effects of these agents have been suggested to be not related to any direct decrease in lipid levels. Multiple mechanisms for these beneficial effects of HMG CoA reductase inhibitors have been proposed, including anti-proliferative effects on mesangial cells [70], reduced glomerular macrophage accumulation mediated by a concomitant reduction in gene expression of monocyte chemoattractant protein-1 (MCP-1), and a reduction in TGF- β 1 gene expression [66, 67, 69]. Although these results may be relevant to a possible beneficial action of HMG CoA reductase inhibitors in diabetic nephropathy, these findings cannot be viewed as conclusive evidence for a renoprotective effect of lipid-lowering intervention *per se*.

Clinical studies

Although lipid-lowering treatments have been shown to be effective in diabetic subjects and to reduce cardiovascular morbidity and mortality in the presence of moderate hyperlipidemia [71], their potential renoprotective properties in diabetic nephropathy as well as in nondiabetic chronic renal diseases remain still controversial.

Nondiabetic chronic renal disease

The efficacy of lipid-lowering treatments and in particular of HMG CoA reductase inhibitors to slow or delay the course of primary nephropathies has not yet been properly assessed in prospective randomized studies. Only a few intervention studies of limited size have attempted to evaluate the effects of lipid-lowering therapy in progression of nondiabetic renal disease.

In seven nondiabetic patients with nephrotic syndrome, Rabelink *et al.* have reported a partial remission of nephrotic syndrome after 48 weeks simvastatin treatment [72]. The investigators observed a significant decrease in proteinuria with an increase in serum albumin but no changes in serum creatinine. However, there was no parallel untreated control group. These findings are similar to those reported by Neverov *et al.* who found a significant beneficial effect of lovastatin treatment on both proteinuria and serum albumin level in 20 non diabetic nephrotic patients [73].

A prospective clinical trial has compared the renal effects of simvastatin with a low cholesterol diet treatment versus diet alone in 17 patients with idiopathic membranous nephropathy and nephrotic syndrome. After a mean follow-up of 19 months, total cholesterol and LDL-cholesterol were significantly reduced in the statin group. Simvastatin treatment was associated with a 75% decreased in proteinuria, as assessed by the urinary protein/creatinine ratio, and a concomitant increase in serum albumin concentration [74]. Low cholesterol diet alone failed to improve the lipids level and did not consistently reduce urinary protein excretion. However, no difference between the two groups in the rate of decline in renal function, as assessed by

serum creatinine and radio labelled EDTA clearance, was observed [74]. More recently, preliminary data have shown that three-months treatment with probucol, an antioxidant that lowers plasma cholesterol, reduced urinary protein excretion in 15 patients with long-standing membranous nephropathy and nephrotic syndrome [75].

Prospective randomized intervention studies are required to better ascertain whether lipid-lowering therapy may have a beneficial effect on progression in nondiabetic chronic renal disease.

Diabetic nephropathy

Initial uncontrolled studies suggested a beneficial effect of the HMG CoA reductase inhibitor pravastatin on progression of albuminuria [76, 77]. But as shown in *Table I*, most of the placebo-controlled and cross-over studies with HMG CoA reductase inhibitors have reported no or only a minimal effect on proteinuria over weeks to months in both type 1 and type 2 diabetes (*Table I*) [76-84]. Only a few studies have been conducted over at least 12 months. In a prospective single blind placebo-controlled study, Lam *et al.* showed in type 2 diabetic patients that the decline in renal function (assessed by GFR) was significantly attenuated by lovastatin treatment, in comparison to placebo after 2 years of treatment [78]. However the 24 hour albumin excretion rate and serum creatinine levels increased in both groups and the statistical analysis applied in that study has been disputed [85].

Furthermore, this study included a relatively heterogeneous group of 34 patients with either micro or macroproteinuria, making it difficult to determine if

TABLE I. *Effects of lipid-lowering therapy on progression of albuminuria in diabetic subjects with micro and macroalbuminuria.*

Type of diabetes	Agent used	N	Duration	Effect on albuminuria	Reference
Microalbuminuric stage					
Type 1	pravastatin	20	12 weeks	→	Zhang et al. [81]
Type 1	simvastatin	22	18-30 weeks	→	Barnes et al. [82]
Type 2	simvastatin	18	36 weeks	→	Nielsen et al. [83]
Type 2	simvastatin	19	1 year	↓	Tonolo et al. [79]
Type 2	gemfibrozil	15	1 year	↓	Smulders et al. [84]
Macroalbuminuric stage					
Type 1	simvastatin	26	12 weeks	→	Hommel et al. [80]
Type 2	pravastatin	19	12 weeks	↓	Sasaki et al. [76]
Type 2	pravastatin	12	12 weeks	↓	Shoji et al. [77]
Type 2	lovastatin	34	2 years	↑	Lam et al. [78]

the findings are relevant to patients with early and/or advanced nephropathy.

In a cross-over study with one year simvastatin treatment period, Tonolo *et al.* have shown in moderately hypercholesterolemic microalbuminuric type 2 diabetic patients with normal renal function that simvastatin significantly decreased plasma total and LDL cholesterol levels. This lipid-lowering effect was associated with no changes in renal function but a concomitant 25% decrease in albuminuria and a rebound in albuminuria after cessation of simvastatin [79]. These results must be interpreted with caution since only 19 patients were included. By contrast, no similar benefit of HMG CoA reductase inhibitor has been observed in several studies in type 1 [80, 81, 82] and type 2 diabetes [83].

One randomized controlled trial has specifically evaluated the triglyceride-lowering effects of a fibrate on progression of microalbuminuria in diabetic nephropathy [84]. Fifteen normotensive type 2 diabetic patients with both hypertriglyceridemia and microalbuminuria received either placebo or gemfibrozil over 12-months. Lipid-lowering treatment was associated with an improvement in hypertriglyceridemia, and progression of albuminuria was reduced, albeit not statistically significant, in the gemfibrozil treated subjects when compared to the placebo group. In comparison to patients with stable or increasing triglyceride levels, the subgroup with a marked reduction in triglyceride concentrations had a significant lower rate of progression of albuminuria [84]. This preliminary yet small study supports a potential specific benefit of triglyceride-lowering therapy on the progression of albuminuria in diabetic nephropathy but requires confirmation by a larger randomized trial of longer duration.

In summary, these trials of relatively short duration have primarily evaluated the effects of lipid-lowering treatment on progression of albuminuria, which must be considered as a surrogate end-point for diabetic nephropathy since the major aim of such treatment is to postpone or prevent end-stage renal failure [86]. Only the study by Lam *et al.* has demonstrated any significant effect of lipid-lowering therapy on renal function. In all of these trials, the patient numbers were too small and the duration of follow-up was too short for assessing adequately the development of a chronic pathological disease for which the rate of progression is highly variable.

CONCLUSION

Dyslipidemia in diabetic patients has been clearly demonstrated to be an important risk factor for the development of atherosclerosis and vascular disease. In addition, a range of experimental and clinical studies suggest that serum cholesterol may play a significant independent role in the development of diabetic

nephropathy. The potential influence of serum cholesterol on the subsequent decline in renal function and/or the progression of albuminuria in diabetic nephropathy remains controversial and needs to be examined in more detail in larger clinical studies of longer duration. Previously, trials have used surrogate end points, such as albuminuria which are inadequate for assessing retardation or prevention of chronic renal impairment. Prospective studies, in particular with lipid-lowering therapy, are now required to carefully determine the role of serum lipids in the development and the progression of diabetic nephropathy. These studies would assist in clarifying whether HMG CoA reductase inhibitors should be considered as additional renoprotective agents in diabetic nephropathy.

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