LIPIDS, PROTEIN INTAKE, AND DIABETIC NEPHROPATHY

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SUMMARY
Progressive impairment of kidney function is one of the major problems in diabetic patients. Control of glycaemia and blood pressure is the main strategy for preventing or slowing impairment in renal function in this condition. However, contributing factors such as hyperlipidaemia and high protein intake have now been identified, and their control can be regarded as a complementary measure. The role of lipid abnormalities and hypercholesterolaemia in the pathogenesis of glomerular injury has been demonstrated in animal models, and a link between hypercholesterolaemia and diabetic nephropathy has been established in humans. To date, few intervention studies in diabetic patients have shown a slower decline in renal function. Nonetheless, in every study in which follow-up was long enough, cholesterol lowering had a beneficial effect on renal function. Although hypercholesterolaemia may not be the cause of renal injury, it represents an aggravating factor. High serum cholesterol seems to have a similar action on glomerular mesangial cells and endothelial cells. This appears to be analogous to the process of atherosclerosis, as mesangial cells possess binding sites for LDL and oxidised LDL, help recruit macrophages and secrete proliferative factors. Protein intake is another factor that can influence renal deterioration. Two meta-analyses have confirmed the beneficial effect of a low-protein diet in diabetic nephropathy, showing no adverse effects on the glycaemic control. Protein intake even seems to enhance the sensitivity of tissues and liver to insulin. Thus, there appear to be no contraindications to such diets in well-controlled diabetic patients. In short, although glycaemic and blood pressure control are still the main lines of treatment for diabetic patients, lowering blood cholesterol and restricting protein intake represent complementary measures that can help slow renal impairment.

Key-words: diabetic nephropathy, hypercholesterolaemia, protein intake.

RÉSUMÉ
La dégradation progressive de la fonction rénale chez le patient diabétique est une préoccupation médicale essentielle. Le contrôle glycémique, ainsi que le contrôle tensionnel, ont fait preuve de leur efficacité pour moduler l’évolution de cette dégradation. Cependant, la dernière décennie a mis en évidence d’autres facteurs, tels le dysmétabolisme lipidique ou l’apport protéique excessif. Le rôle des anomalies lipidiques et de l’hypercholestérolémie en particulier dans la pathogenie des lésions glomérulaires est connu depuis longtemps et a été démontré au niveau des modèles animaux. L’hypercholestérolémie semble un co-facteur et non pas le facteur causal, par contre sa participation à l’évolution de la néphropathie chez le patient diabétique semble démontrée. Dans de nombreuses études, le taux de cholestérol à l’entrée dans l’étude est un élément prédictif de l’évolution de la fonction rénale 10 ans plus tard. Par ailleurs, les études d’intervention semblent bien montrer qu’en réduisant la dyslipidémie, on ralentit l’évolution de la progression de l’insuffisance rénale. Enfin, la cellule mésangiale semble se comporter de façon analogue à la cellule endothéliale, rappelant les mécanismes impliqués dans l’athérosclérose avec participation des LDL oxydés, recrutement des macrophages et sécrétion de facteurs de prolifération. La charge protéique nutritionnelle est un autre facteur susceptible d’influencer la détérioration de la fonction rénale. Deux méta-analyses confirment qu’un régime restrictif en protéines est susceptible de ralentir l’évolution de la dégradation de la fonction rénale. Parallèlement, il est rappelé que l’insuffisance rénale est associée à un certain degré d’insulinorésistance et que la restriction protéique est un des moyens de lutter contre cette insulinorésistance, tant au niveau périphérique qu’au niveau hépatique. Dans ces conditions, il apparaît qu’il n’y a aucune contre indication à prescrire une diététique restrictive en protéines, tant sur le plan néphrologique, que sur le plan diabétologique, particulièrement chez le patient diabétique non insulinodépendant. Au total, même si le contrôle glycémique et la tension artérielle restent les moyens essentiels pour moduler l’évolution de la fonction rénale, le contrôle du métabolisme lipidique, ainsi que la restriction de l’apport protéique sont des mesures complémentaires susceptibles de ralentir la dégradation de la fonction rénale.

Mots-clés : néphropathie diabétique, hypercholestérolémie, apport protéique.

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Although progressive impairment of kidney function is one of the major problems in diabetic patients, it can be delayed by anti-hypertensive therapy [1] and may be influenced by the quality of metabolic control [2]. Hypertension and glycaemic control are the major factors affecting progression of impairment in renal function in diabetic patients, but other factors have been identified over the last decade, including hyperlipidaemia and protein intake (apparently the most important ones). Although the exact role of these factors is difficult to establish, they should not be overlooked since a judicious combination can slow decline in renal function in diabetic patients. As a result of improved life expectancy and the greater frequency and earlier onset of Type 2 diabetes, protection of renal function is of increasing concern.

## RELATIONSHIPS BETWEEN LIPID ABNORMALITIES AND KIDNEY DISEASE

Lipid deposits in histologic sections of kidneys from patients with chronic renal disease were described by Virchow in 1860 [3]. However, Morehead et al. [4] only recently (1982) suggested that lipid nephrotoxicity may exacerbate renal disease rather than be a consequence or a primary initiator of it.

### Animal studies

The role of lipid abnormalities in the pathogenesis of glomerular injury has been demonstrated in experimental renal diseases [5]. Diet-induced hypercholesterolaemia in Sprague Dawley rats, guinea pigs and New Zealand white rabbits was associated with premature development of glomerulosclerosis and a more rapid progression of albuminuria and focal glomerulosclerosis as compared to rats fed normal chow [6, 7]. A similar exacerbation of chronic amino-nucleoside nephrosis by dietary cholesterol supplementation has been reported [8]. Moreover, rats subjected to experimental renal damage (5/6 nephrectomised model) developed systemic HTA, hypercholesterolaemia and progressive renal injury [9]. When these animals were treated with a lipid-lowering agent, secondary hypercholesterolaemia was prevented and there was a reduction in glomerular injury independent of glomerular pressure [10]. In a model of endogenous hyperlipidaemia (Zucker rats), which is similar to that seen in Type 2 diabetic patients, pharmacological lowering of serum lipids was found to attenuate renal injury [11].

Experimental studies point to an important role for abnormal lipid metabolism in the progression of renal disease. Dietary-induced hypercholesterolaemia produces relatively modest glomerular injury. However, in the presence of a reduced nephron population or underlying renal diseases, nephron injury can be exacerbated by hypercholesterolaemia, and lipid-lowering agents attenuate the progression of the disease.

### Human studies

Despite experimental evidence of lipid nephrotoxicity, patients with primary dyslipidaemia do not appear to have an increased incidence of renal disease. Smellie and Warwick [12] found no higher prevalence of microalbuminuria in these patients. There are only a few conditions of abnormal lipid metabolism accompanied by renal failure. For example, patients with LCAT deficiency have lipid deposits in kidney cells together with foam cells associated with mesangial expansion and glomerulosclerosis [13]. In non-diabetic patients with proteinuria, hypercholesterolaemia and HTA, the rate of loss of renal function was nearly twice that of patients without marked hyperlipidaemia [14]. This effect was independent of blood pressure control.

It has been suggested that lipids may act synergistically in the progression of renal injury [15]. Interestingly, lipid-lowering treatment (simvastatin) has been reported to improve albuminuria [16].

### LIPID ABNORMALITIES AND DIABETIC NEPHROPATHY

#### Animal models

Studies on animal models of diabetic nephropathy indicate that raised levels of serum lipids can damage glomeruli or accelerate the loss of renal function. The Zucker rat is a strain which suffers from genetic obesity, hyperlipidaemia and insulin resistance. These rats also develop glomerular segmental sclerosis and hyperlipidaemia, which appear to play a role in the progression of nephropathy [6].

#### Human studies

A large number of studies have established a relation between hypercholesterolaemia and nephropathy in diabetic patients. In 31 Type 1 diabetic patients followed up over 18 months, in whom kidney function was evaluated by Cr$^{51}$ EDTA, Mulec et al. [17] showed that mean cholesterol concentration at entry ($7.4 \pm 1.9$ mmol/l) into the study was significantly correlated with decline in the glomerular filtration rate ($R = 0.40$. Spearman’s rank correlation $p < 0.05$). Mean cholesterol throughout the study was also correlated with the rate of progression ($R = 0.44$. $p < 0.05$). When patients were divided into two groups according to mean cholesterol level (either below or above 7 mmol), the decline in GFR was much more...
striking in the high cholesterol group (decline in GFR m/\text{min/}\text{year} = 8.4 \pm 5.3) than in the low cholesterol group (2.3 \pm 6.3 \text{ mmol/min/}\text{year}) (p < 0.01). On the basis of stepwise regression analysis in a prospective follow-up of Type 1 diabetic patients, these authors found a significant correlation between initial values for serum total cholesterol (r = −0.61 p < 0.01), triglyceride (r = 0.48 p < 0.01) and apo B (r = −0.39 p < 0.05) and the subsequent decline in GFR during the 2.5-year follow-up [18]. In 18 patients with IDDM followed up for one year, Parving et al. [19] also established a significant relationship between the ratio of decline in GFR and total cholesterol (r = 0.51 p < 0.05).

All patients recruited in the Diabetes Retinopathy Study had diabetes and a confirmed diagnosis of proliferative retinopathy [20]. To investigate the role of hypercholesterolaemia as a determinant of renal function, the authors of this study only considered patients who had developed diabetes before age 30 and were treated with insulin. A total of 439 Type 1 patients with nephropathy were followed up over a 3-year period. To identify determinants of rapid loss in renal function, the study group was divided into subgroups: non-progressors, slow progressors, and rapid progressors. All subgroups had a similar serum creatinine at entry, suggesting that the different rates of decline of renal function were unrelated to baseline creatinine. The subgroups differed at entry in serum cholesterol and blood pressure. For a cholesterol level between 180 and 219 mg/dl, around 25% of the patients suffered a rapid loss in renal function. At 220–259 mg/dl, this rose to 32%, at 260–299 mg/dl to 38%, and nearly half (48%) of those with a cholesterol above 300 mg/dl had a similar fate. The relation between the prevalence of rapid progression and the level of serum cholesterol was statistically significant. These data are of particular interest since the patients were studied prospectively between 1972 and 1979 when antihypertensive therapy was not often used, thus ruling out its potential influence on lipid levels.

In the Wisconsin study [21], a population-based cohort of individuals with earlier onset diabetes (< 30 years old and insulin-treated), 634 patients were followed-up over ten years. Age, duration of diabetes, HbA1c, and systolic blood pressure were found to be risk factors for the decline in creatinine clearance. Interestingly, total cholesterol (p < 0.05) was also significantly related to the estimated annual decrease in creatinine clearance. HDL cholesterol was inversely related to the incidence of renal insufficiency.

Thus, prospective studies over the last decade have established a relation between the level of total cholesterol and a decline in GFR and creatinine clearance in Type 1 diabetic patients.

In Type 2 diabetic patients, the results are more difficult to interpret as this disease is multifactorial (insulin-resistance, HTA, obesity, dysmetabolism).

Silveiro et al. [22] noted a positive correlation between plasma cholesterol and glomerular hyperfiltration in Type 2 patients with proteinuria, whereas Jerums et al. [23] found no difference in total cholesterol in such patients, regardless of the progression of renal albuminuria over an 11-year period. Yokota et al. [24] also failed to find any correlation in 54 Type 2 patients, but all of them were older than 71 years. In a five-year observation of 94 Type 2 patients, Haslacher et al. found a positive correlation between decline of renal function and triglycerides, but not cholesterol [25].

In an attempt to identify some of the confounding factors, Ravid et al. [26] studied 94 Type 2 diabetic patients with microalbuminuria of 30 to 300 mg/dl, who were examined every three months for five years and randomised to receive either enalapril (10 mg/ day) or placebo. In the placebo group, there was a 13% decline in reciprocal creatinine values over the five years, and the decline in renal function could be predicted by the initial total cholesterol level (r = 0.783 p < 0.001) as well as by initial blood pressure, HbA1c and albuminuria. In the enalapril-treated group, there was only a marginal decline in renal function (1% for five years), but in each case it was correlated with initial total cholesterol (0.735 p < 0.001) and remained significant when the influence of blood pressure was eliminated. Hypercholesterolaemia is therefore an independent risk factor for the subsequent worsening of nephropathy in Type 2 diabetic patients. However, elevated lipid level may have been secondary to urinary loss of albumin. In the placebo group, the correlation between changes in plasma cholesterol and creatinine was not altered when controlled for the influence of albuminuria.

In another study [27], initial cholesterol was highly predictive (multiple R value = 0.568 p < 0.001) of subsequent decrease in renal function in 404 Type 2 patients over a 7.8-year follow-up period. Total cholesterol thus seems to be an independent risk factor for subsequent decrease in renal function, although this will need to be confirmed in prospective studies of appropriate corrective treatments.

No correlations of LDL subclasses [28] and Lpa [29] with the course of renal function have been found in diabetic patients. The relation between apolipoprotein E polymorphism and renal function has been investigated. In one study [30], apo E2 allele frequency was significantly higher in diabetic patients (9.6%) than in patients without renal failure (3.2%) or control non-diabetic patients (3.7%). In another study [31], the E2 allele was found to be a negative predictor for creatinine clearance and a positive predictor for urinary excretion of albumin. As there is a relation between apo E polymorphism and lipoprotein metabolism, apo E may also be involved in renal damage in Type 2 diabetic patients.
EFFECT OF CHOLESTEROL-LOWERING AGENTS ON RENAL FUNCTION IN DIABETIC PATIENTS

In the Diabetic Retinopathy Study, Krolevsky et al. [20] found a significant correlation between loss of renal function in 439 Type 1 diabetic patients and mean blood pressure and total serum cholesterol at entry. The authors concluded that loss of renal function could be prevented in up to 50% of patients by maintaining diastolic blood pressure below 85 mmHg and total cholesterol below 220 mg/dl. However, the correlation between cholesterol and loss of renal function is not an indication of a cause-effect relationship. The results of appropriate therapeutic interventions will be required before it can be concluded that high cholesterol exacerbates renal impairment in these patients. Despite an extensive literature on the safety and efficacy of various anti-lipid treatments in diabetic patients, few studies have examined their effect on the progression of nephropathy, although the results of trials in animal models are encouraging. Obese Zucker rats, a model for Type 2 diabetes, develop glomerular mesangial expansion and albuminuria at 14 weeks of age and focal segmental sclerosis at 28 weeks that mimic diabetic sclerosis. Treatment of hyperlipidaemia with lovastatin and clofibrate acid, starting at 8 weeks, reduced serum cholesterol and largely prevented the development of mesangial expression and glomerular sclerosis [11]. The use of lovastatin to retard the progression of established nephropathy in Zucker rats has also been beneficial [32]. Lovastatin given at 26 weeks, when glomerular lesions and albuminuria are already well-established, prevented a further rise in albuminuria and arrested the subsequent development of glomerular sclerosis.

Few clinical trials have been conducted in human diabetic patients. Sasaki et al. [33] examined the effect of 12 weeks of treatment with pravastatin (10 mg) in nine patients with Type 2 diabetes. The urinary albumin/creatinine ratio decreased with treatment in these patients with macro- or microalbuminuria. A reduction of albuminuria in Type 2 diabetes following treatment by pravastatin was also shown in a study reported by Shoji et al. [34]: 12 Type 2 patients with hypercholesterolaemia were given 10-20 mg pravastatin daily for 12 weeks. The urinary albumin/creatinine ratio significantly decreased from a mean of 49 to 20 mg/g. These two studies provide evidence that treatment with HMG CoA reductase inhibitors attenuates lipid-induced glomerular injury in Type 2 patients, as indicated by a reduction in albuminuria.

In a double-blind randomised and placebo-controlled study, Nielsen et al. [35] investigated the effect of simvastatin (10-20 mg/day) for 36 weeks on kidney function and urinary albumin excretion in 18 Type 2 diabetic patients with persistent microalbuminuria and moderate hypercholesterolaemia. GFR was measured by the plasma clearance of Cr\textsuperscript{51}-EDTA. Although dyslipaemia was markedly improved with simvastatin in diabetic patients and GFR was reduced and UAE increased in the placebo group (without any changes in the simvastatin group), these developments did not reach significance. The authors concluded that lipid-lowering had no impact on kidney function in diabetic patients. However, it could be argued that the follow-up was too short to provide a clear-cut effect.

Lam et al. [36] investigated the effect of lovastatin (20 mg/day) on the progression of diabetic nephropathy in a larger population (34 Type 2 patients) over a longer period (2 years). Patients were randomly assigned to lovastatin or placebo. Their serum creatinine was < 120 mmol/l, fasting cholesterol was above 5.2 (but less than 7.8 mmol/l), and proteinuria was greater than 0.15 g/day. Renal function was assessed by serial measurement of serum creatinine, GFR (Cr\textsuperscript{51}-EDTA) and 24-h urinary protein excretion. Lovastatin was associated with a significant reduction in total LDL cholesterol. GFR deteriorated significantly in the placebo group after 24 months (~ 2.76 ml/min/1.73 m\textsuperscript{2} at 12 months and ~ 10.85 ml/min/1.73 ml at 24 months), but showed no significant change in the lovastatin-treated group (~ 2.9 mmol at 12 months and ~ 2.03 at 24 months). In a two-year double-blind cross-over study of the effect of simvastatin on the urinary albumin excretion rate [37], 19 normotensive microalbuminuric (microalbumin between 30 and 100 mg/24 h) and hypercholesterolaemic (total cholesterol > 6.2 mmol/l) Type 2 diabetic patients were treated with simvastatin (20 mg) or placebo. Simvastatin significantly decreased plasma cholesterol (total and LDL), which was accompanied by a significant decrease in AER (25% from basal). No changes were observed in cholesterol levels during placebo treatment, which was accompanied by an increase in AER. No changes in creatinine clearance were observed with either treatment.

Thus, therapeutic lowering of cholesterol (HMG CoA reductase inhibitor) over a long period seems to slow the decline of GFR and the progression of AER.

MECHANISMS BY WHICH HYPERLIPIDAEMIA AND LIPID-LOWERING AGENTS INFLUENCE RENAL FUNCTION

Mesangial cell proliferation, which has been demonstrated in many experimental renal diseases [38], is a response of glomerular mesangial tissue to injury that contributes to glomerulosclerosis. After injury, growth factors (PDGF, EGF) contribute to the proliferation of mesangial cells which secrete these factors by an autocrine mechanism.

Analogy with the pathologic processes involved in the development of atherosclerosis and the changes leading to glomerulosclerosis has focused attention on potentially common risk factors such as HTA and...
hyperlipidaemia [39]. Abnormal lipid accumulation has been documented in various forms of non-diabetic glomerular diseases [40], and foam cells have been identified in glomeruli as well as in renal interstitium.

Following initial glomerular injury, macrophage and macrophage-derived proinflammatory products may give rise to deleterious effects leading to glomerular mesangial cell proliferation and increased mesangial matrix biosynthesis, which both participate in glomerulosclerosis. The pathological features of glomerulosclerosis, akin to those of atherosclerosis, have been reviewed by Diamond and Karnovsky [39]. Mesangial cells are closely related to vascular smooth muscle cells in term of origin, microscopic anatomy, histochemistry and contractility [39]. They harbour receptors for both LDL and oxidised LDL [41, 42], and uptake of oxidised LDL by mesangial cells plays a role in the recruitment of macrophages into the glomeruli, akin to that described in atherogenesis [43]. They may also contribute to macrophage infiltration via the release of colony-stimulating factor (CSF) and monocyte chemoattractive peptide [44]. Moreover, it has been demonstrated [45] that exposure of cultured mesangial cells to LDL increases their expression of PDGF mRNA. In the same way, incubation of mesangial cells with LDL progressively increases the fibronectin content of supernatant in a dose-dependent manner, and is accompanied by an increase in fibronectin mRNA [46]. The uptake of oxidised LDL may stimulate eicosanoid synthesis, leading to haemodynamic abnormalities [47]. These cells also release cytokines and growth factors which may stimulate their proliferation [48]. TGFβ induces matrix synthesis by mesangial cells and decreases the production of metalloprotease [49].

It can thus be seen that glomerulosclerosis shares a common pathogenesis with atherosclerosis, involving LDL and oxidised LDL uptake by specific receptors on mesangial cells, monocyte influx and subsequent formation of foam cells, deposition of apolipoprotein [50, 51], and accumulation of lipids. The specific uptake of LDL can thus amplify and accelerate the processes leading to mesangial cell proliferation, matrix production and glomerulosclerosis [52].

Other mechanisms, such as intrarenal haemodynamic alterations, have been proposed. For example, glomerular capillary pressure was increased by 10-20% in rats fed a high cholesterol diet compared to those fed a standard diet [6, 53]. Physical factors such as whole blood rheology and plasma viscosity, which are known to be increased in patients with hypercholesterolaemia [54], may also be involved. Moreover, vasoactive factors may be released owing to the increased number of mesangial cells and macrophages induced by cholesterol feeding [55].

Lipid-lowering drugs have been shown to attenuate renal damage in diabetic patients. Although a direct influence on lipid levels cannot be ruled out, both simvastatin and lovastatin have been shown to exert a direct intracellular action on the mevalonate pathway. It has been demonstrated in mesangial cultured cells that lovastatin inhibits PDGF-induced mesangial cell mitogenesis and that this inhibition is reversed by mevalonate or farnesil phosphate (a metabolite of mevalonate) [56]. Lovastatin has also been shown to inhibit both MCP1 and IL6 mRNA expression and secretary protein in a dose-dependent manner [57]. Thus, lovastatin appears to have a beneficial effect on mesangial cells independently of its cholesterol lowering-effect [58], indicating that the mevalonate pathway may play a role in mesangial damage in diabetes.

**Influence of Protein Restriction on the Progression of Diabetic Renal Failure**

It has long been known that high protein intake worsens the clinical manifestations of patients with renal insufficiency. Several studies in the last decades have also indicated a potentially harmful effect of dietary protein on renal function and structure in animals with renal lesions [59]. Clinical studies in both diabetic and non-diabetic patients have so far failed to demonstrate a beneficial action of protein restriction. In view of the difficulties of dietary compliance in diabetes, patients and doctors alike have tended to assume that protein restriction would not slow the progression of renal impairment. However, over the last five years, evidence has accumulated that this type of diet is effective [60]. A meta-analysis by Fouque et al. [61], which included 890 patients from six controlled studies, most of whom were without diabetic renal disease, showed that dietary protein restriction reduced the risk of renal failure. However, inconclusive results were reported from a large multicentre randomised trial in the Modification of Diet in Renal Disease (MDRD) study [62], which divided patients into two groups. The first group of 585 patients with a glomerular filtration rate of 25-55 ml/min/1.73 m² was randomly assigned to a usual protein diet or a low-protein diet (1.3 or 0.58 g of protein/kg body weight) and to a usual or a low blood pressure treatment (mean arterial pressure 107 or 92 mmHg). A second group of 255 patients with a GFR of 13-24 ml/min/1.73 m² was randomly assigned to a low or very low protein diet (0.58 or 0.28 g protein/kg body weight) with a keto-amino acid supplement and usual or low blood pressure treatment. GFR was measured on the basis of renal clearance of 125I iodothalamate over 18 to 45 months. In the first group, the mean rate of decline in GFR/ml/min/year was 4.5 in the low-protein, usual pressure group, 3.3 in the usual protein, low-pressure group, and 2.8 in the low-protein, low-pressure group. Overall, there was a 28-29% reduction in the rate of decline of GFR in patients with low-
proteins or blood pressure-lowering treatment, with an additive effect of the two treatments, although the figures did not reach statistical significance. No differences were demonstrated for the second group with the very low protein diet. The data for the MDRD study were revisited in 1996, taking into account the true protein intake of patients. The correlation analysis showed that, over a range of protein intake of 0.5 to 1.0 g/kg/d, lower protein intake was associated with slower decline in GFR and a longer interval until the onset of renal failure [63]. Therefore, the authors proposed an intake of 0.6 g/kg/d of protein for patients with renal disease.

Another meta-analysis and separate meta-analyses of studies in diabetic and non-diabetic patients, including those of the MDRD study, were reported by Pedrini et al. [64]. Out of 38 studies, only five used a randomised controlled design and had a mean length of follow-up of more than one year. These five studies accounted for a total of 1,413 patients, including 108 identified as Type 1 diabetic patients. The prescribed protein intake in the low-protein diet group ranged from 0.4 g/kg to 0.6 g/kg body weight. All five studies concluded that the low-protein diet had a beneficial effect in the diabetic group. The pooled results showed that dietary protein restriction significantly reduced the risk for decline in GFR, creatinine clearance, or urinary albumin excretion (relative risk 0.56, confidence interval 0.40 to 0.77, p < 0.001). Similar results were observed for non-diabetic patients, and Pedrini et al. concluded that dietary protein restriction effectively slowed the progression of both diabetic and non-diabetic renal diseases.

Although these results indicate that protein restriction was effective in diabetic nephropathy, nephrologists and diabetologists are somewhat reluctant to prescribe a low-protein diet for diabetic patients with renal disease because an additional dietary restriction may be intolerable for them. Moreover, the implementation of dietary recommendations for diabetic patients over the last few years has resulted in a high protein intake in these patients. In the Euro-Diab Type 1 study, Toller et al. [65] evaluated nutritional intake in 2,968 Type 1 patients from 30 centres in Europe and reported a protein intake exceeding 1.2 to 1.3 g/kg body weight/day. Thus, such a diet may contribute to progression of renal disease.

On the other hand, renal failure itself affects carbohydrate metabolism (recently reviewed by Alvestrand [66]). Peripheral insulin resistance, hepatic glucose production, and insulin clearance rate have also been found to be altered in patients with chronic renal failure. Moreover, it has been shown that a low-protein diet has a corrective effect on these alterations [67-69]. There now seems to be sufficient evidence to allow diabetologists and nephrologists to prescribe a low-protein diet to their diabetic patients, although diabetologists need indications that a high-protein diet precipitates renal disease, while nephrologists must be sure that a low-protein diet with an increase in carbohydrate intake will not deteriorate glycaemic control.

Because of the reduction in protein intake, the proportion of carbohydrates or fats must be increased. As mentioned above, there are abundant reasons for not increasing fat intake, but there may also be harmful effects of increasing carbohydrates. Interestingly, studies have shown that both short- and long-term increases in carbohydrate intake are accompanied by an improvement in insulin action. In patients with chronic renal failure without diabetes, it is thus appropriate to compensate for the reduction in protein caloric intake by carbohydrate calories. Our experience using diets providing 0.5 g/kg body weight of proteins supplemented with keto-analogs, and with carbohydrates providing 60-68% of the total caloric intake, have confirmed the beneficial effect on insulin action [67]. Determination of insulin sensitivity with the euglycaemic hyperinsulinaemic clamp technique with indirect calorimetry and the use of stable tracers allowed us to show that non-diabetic patients with chronic renal failure (who were subjected to protein restriction and whose caloric loss was made up by carbohydrate calories) experienced general improvement in insulin sensitivity in both tissues and liver as well as in oxidative and non-oxidative glucose metabolism. These results are encouraging, even for non-diabetic patients, since subjects with chronic renal failure tend to develop an insulin-resistance syndrome leading to hyperinsulinaemia and ultimately to increased risk of cardiovascular morbidity.

These observations suggest that a similar reasoning applies to patients with insulin resistance before the onset of renal failure, which is precisely the situation of those with Type 2 diabetes. This implies that protein restriction and augmentation of carbohydrate intake would slow the course of chronic renal failure in Type 2 patients. Furthermore, regardless of renal function, this strategy would also tend to improve the metabolic stability of these patients.

A similar management of patients with Type 1 diabetes would have the same consequences, except for a reduction in insulin needs despite increased carbohydrate intake [70, 71]. This reduction in insulin requirement reinforces the effect of the diet on the peripheral action of insulin, but may not always lead to improvement in the control of diabetes because it leaves less room for manoeuvres in insulin dosage, adding to the subtlety of its use.

Overall, the diabetic patient not suffering from chronic renal failure learns that carbohydrate intake must be strictly observed. He is instructed that quickly absorbed carbohydrates should be consumed in moderation, while complex carbohydrates are crucial to metabolic stability and must therefore form an essential part of his diet. The same patient learns from his
diabetologist that fat reduction is harmful for the walls of his arteries and ultimately for his metabolic equilibrium, especially if he has Type 2 disease. When the same patient later consults with chronic renal failure, the nephrologist proposes a reduced protein intake adapted to the glomerular filtration of the patient. In view of the general composition of food, protein restriction is usually associated with restriction in fats, and the caloric deficit must be compensated by an increase in carbohydrates. When he sees his usual ration of carbohydrates increase, the patient may lose his bearings with respect to his former eating habits and the initial advice of his doctors. Nevertheless, this new advice does not contradict the previous recommendations since an increase in carbohydrate intake without modification of total caloric intake is by no means detrimental to glycaemic control.

Diabetic patients with chronic renal failure should therefore be managed by protein restriction, with the loss in calories being compensated by carbohydrates and not by fat. This augmentation in carbohydrates should have no detrimental effect on the patient’s diabetes, but management calls for close collaboration between the two specialists so that the patient does not feel that one disease is being treated at the expense of the other.

However, when a low protein diet is prescribed, the nutritional status of the patient must be carefully monitored, as the slowing of the course of renal failure should not be at the expense of malnutrition [72]. We have demonstrated that a low-protein diet is associated with an increase in basal energy expenditure [73], so that a follow-up by a dietician at monthly intervals is appropriate. The metabolic status of diabetic patients also needs to be satisfactory since anabolism is compatible with insulin therapy and a normal plasma glucose level, whereas a relative insulin deficit and a poorly controlled blood glucose level lead to catabolism. Low-protein diets should thus be restricted to well-controlled diabetic patients.

## CONCLUSION

Nephropathy now represents a significant problem in diabetic management, and the prevention or slowing of the decline in creatinine clearance is an important objective in order to avoid end-stage renal disease. A number of factors involved in the progression of diabetic nephropathy have been identified. Parving et al. [19] prospectively followed up 18 Type 1 diabetic patients for a duration of 8.0 years, with an assessment of glomerular filtration rate every six months by $^{51}$Cr-EDTA. Univariate analysis revealed a significant correlation between the rate of decline in GFR and mean arterial blood pressure, albuminuria, HbA1c and serum total cholesterol.

As HTA and albuminuria accounted for two-thirds of the variation, they are the predominant factors to treat, although plasma lipid levels and protein intake should not be overlooked. Plasma lipid levels can be reduced by drug treatment, but dietary protein restriction attenuates the progression of renal disease and also has an effect on serum lipids in chronic renal failure. Metabolic management (lipid lowering, reduced protein intake) thus forms part of the therapeutic strategy for prevention of diabetic renal failure.

Although lipid lowering and reduction of protein intake may ward off the onset of chronic renal failure, their effects require time, and metabolic management needs to be instigated early and well before end-stage kidney disease.

### REFERENCES


