Remission of Proteinuria Following Correction of Hyperlipidemia in NIDDM Patients With Nondiabetic Glomerulopathy

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OBJECTIVE — Animal studies suggest that hyperlipidemia may play a direct role in glomerular damage. In patients with non-insulin-dependent diabetes mellitus (NIDDM), dyslipidemia occurs early in the course of nephropathy and may be involved in the progression of renal disease.

CASES — We report on two young NIDDM patients with marked hyperlipidemia and proteinuria, in whom renal biopsy demonstrated nondiabetic glomerulopathy. In both cases, the decrease in blood lipid levels was associated with a major decrease in proteinuria. Episodes of hyperlipidemia were associated with a resumption of heavy proteinuria in one patient with serum triglyceride levels and proteinuria being closely correlated.

CONCLUSIONS — These two cases suggest that hyperlipidemia has an important role in the pathogenesis of glomerular disease.

Converging data suggest that lipid abnormalities have a role in the pathogenesis or progression of glomerular disease (1). Animals fed a cholesterol-rich diet develop accelerated glomerulosclerosis (2,3), and endogenous hyperlipidemia also leads to glomerulosclerosis in the obese diabetic Zucker rat (4). In this model, very-low-density lipoprotein (VLDL) particles seem to play a pivotal role (5).

In patients with diabetes, whether insulin-dependent diabetes mellitus (IDDM) (6) or non-insulin-dependent diabetes mellitus (NIDDM) (7), serum cholesterol and triglyceride levels are higher in those with incipient nephropathy, i.e., increased urinary albumin excretion (UAE), than in those with normal urinary albumin levels. These epidemiological studies suggest that lipid abnormalities could play a role in the onset or progression of renal disease in diabetic patients.

In this study, we report on two patients with NIDDM and major hyperlipidemia, in whom nondiabetic glomerulopathy was diagnosed. A close correlation was found between the course of lipid abnormalities and that of proteinuria.

CASES

Case 1

A 43-year-old man (body mass index [BMI] of 26 kg/m^2) with NIDDM showed major mixed hyperlipidemia (Table 1). Thyroid hormone levels were normal, and no xanthomas were found on clinical examination. Blood pressure (BP) was normal. Proteinuria (2 g/day) was present without hypoalbuminemia. Because of the absence of retinopathy, a renal biopsy was performed. There was no apparent change in the 20 glomeruli examined by light microscopy, and tubules and vessels were normal. No deposition of immune complexes or complement was detected by immunofluorescence. Staining of the capillary wall for immunoglobulins or albumin was normal. Electron microscopy was not performed. A low-calorie diet without significant modification of protein intake led to a reduction in fasting serum triglyceride (FTG) and fasting blood glucose (FBG) levels with a corresponding fall in proteinuria (Table 1).

Case 2

A 23-year-old woman was admitted with diabetes and hyperlipidemia. Five years

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VLDL, very-low-density lipoprotein; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; UAE, urinary albumin excretion; BMI, body mass index; BP, blood pressure; FTG, fasting serum triglyceride; FBG, fasting blood glucose; FTC, fasting total cholesterol; GBM, glomerular basement membrane; GFR, glomerular filtration rate.

Table 1—*Course of metabolic parameters, proteinuria, and GFR in two patients with hyperlipidemia and nondiabetic glomerulopathy*

	FBG (mM)	FTG (mM)	FTC (mM)	UAE (g/24 h)	GFR (ml/min)	Body weight (kg)
Patient 1	12.2	40	13	2	153*	78
	18.8	20	9.6	1.5	—	—
	6.5	3.6	5.1	0.25	115*	76
Patient 2	16.8	36	17.7	0.7	—	81.5
	6.2	3.3	9.8	0.18	—	75.3
	23.2	73	18.3	4.4	143*	84
	18.6	37	14	2	149†	83.6
	8.3	4.8	10.4	0.59	111†	78

*Estimated by calculating creatinine clearance. †Measured by EDTA^{51}creatinine clearance.

earlier, metabolic evaluation had only disclosed mild hypertriglyceridemia (FTG of 4.1 mM, fasting total cholesterol [FTC] of 5.1 mM, FBG of 4.2 mM). One year before admission, she was overweight (BMI of 26 kg/m^2). BP was normal. Marked hypertriglyceridemia (36 mM, Table 1) was present with an increase in both low-density lipoprotein and VLDL fractions. Clinical examination did not show evidence of any xanthomas. Thyroid hormone levels were normal. Proteinuria was found on several occasions (0.6–0.7 g/day). On a low-calorie diet controlled for protein intake, the patient's glycemia was normalized, and lipid levels and proteinuria fell (Table 1). Her metabolic status later worsened, and proteinuria increased to the nephrotic range (4.4 g/day) with decreased serum albumin (31 g/l). Tomography showed normal-sized kidneys. In the absence of diabetic retinopathy, a renal biopsy was performed. No specific signs of diabetic glomerulopathy were seen, but two typical glomerular lesions (10%) of focal and segmental glomerulosclerosis were observed. Fibrous synechiae were present, but there were no foam cells. The glomerular lesions were associated with segmental deposits of IgM and C3, but there was no diffuse IgG staining of the capillary wall. In some areas, tubules exhibited hyalin-droplet changes with no atrophic lesions. Vessels were normal. No ultrastructural studies were available. Usual causes of hyalinosis were ruled out. There was no evidence of reflux nephropathy, heroin or analgesic abuse, or HIV infection. During the years that followed, the course of proteinuria varied in parallel with metabolic status (Fig. 1). A correlation was found between proteinuria and FTG measured over a 3-year period (Spearman test, $r = 0.81$, $P < 0.001$).

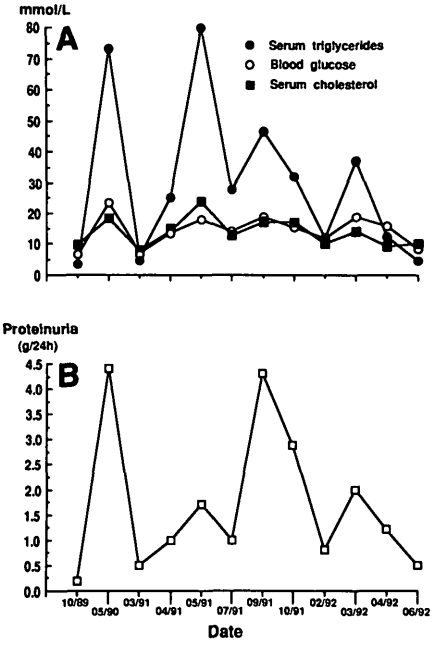

Figure 1—*Parallel course of proteinuria and metabolic parameters in a 23-year-old woman with hyperlipidemia, NIDDM, and nondiabetic nephropathy.*

CONCLUSIONS — In these two patients, nondiabetic nephropathy occurred early in the course of NIDDM and was characterized by parallel changes in proteinuria and lipid levels. Diabetic glomerulopathy was ruled out on the basis of the renal histology in both cases. A variety of nondiabetic nephropathies, which reflect the spectrum of primary glomerular disease and of extrarenal disorders observed in the general population, has been described in up to 30% of proteinuric NIDDM patients who undergo routine renal biopsy (8). In our patients, systemic disorders known to produce glomerular damage were ruled out, and no features of primary glomerulonephritis were discernible on kidney biopsies. Moreover, in these two cases, light microscopy and immunofluorescence did not demonstrate the usual glomerular changes seen in lipoprotein glomerulopathy (9) or the intraglomerular lipid deposits associated with abnormal lipid metabolism as in LCAT deficiency or Alagille's syndrome. Nevertheless, whatever the exact cause of the glomerulopathy, these two patients appear very similar with regard to the parallel course of their metabolic abnormalities and the increased UAE, suggesting that the metabolic abnormalities may have played a direct role in the increased UAE.

Several factors may have participated in the glomerular injury. The involvement of the mild hyperfiltration in the increased UAE cannot be ruled out. Hyperfiltration related to hyperglycemia, which is usual in patients with poorly controlled diabetes, is thought to promote epithelial and endothelial cell injury that may lead, in turn, to hyalinosis and glomerulosclerosis (10). Even if hyperfiltration is not primarily responsible for cell injury, its influence on the rate of urinary protein excretion has been clearly established. Obesity itself is unlikely to have been involved in our patients because it was mild, and proteinuria responded to metabolic improvement in the absence of marked weight loss (11).

Hyperlipidemia is very likely to

have contributed to the glomerular injury in these two patients, given the parallel course of proteinuria and hyperlipidemia. Hyperlipidemia is known to induce glomerular injury in various animal models, and a decrease in serum cholesterol or VLDL triglyceride levels has been shown to reduce glomerular damage and proteinuria in animals (12) and in humans (13).

The mechanisms by which lipids, and particularly lipoprotein particles, lead to renal impairment are unclear. One hypothesis attributes an important role to activated macrophages in a process similar to that of atherosclerosis (3,4). Lipids could also act directly on the glomerular basement membrane (GBM) by altering its phospholipid composition or by attaching to membrane glucosaminoglycans. This would increase GBM permeability, leading to urinary protein leakage. Alternatively, lipids could also produce glomerular hypertension, as reported in hypercholesterolemic rats (4), particularly because they can interact with prostaglandin metabolism and alter vascular resistance.

In conclusion, the onset of proteinuria in the course of NIDDM is not always a manifestation of diabetic nephropathy and may be related to hyperlipidemia. This may have several clinical implications. First, to appreciate the true severity or even the presence of diabetic nephropathy in patients with NIDDM and dyslipidemia, it may be important to reevaluate proteinuria after correction of lipid disorders. Second, a close serial evaluation of blood lipid levels should be included in any trial aiming to evaluate therapeutic efficacy on the course of proteinuria in patients with NIDDM. Third, management of hyperlipidemia in diabetic patients is important, not only for the prevention of macroangiopathy but also for the prognosis of renal disease.

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