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Cholesterol-lowering therapy may retard the progression of diabetic nephropathy

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Summary There is experimental evidence to suggest that hypercholesterolaemia may play a pathogenetic role in progressive glomerular injury. We investigated the effect of cholesterol-lowering therapy on the progression of diabetic nephropathy in 34 patients with non-insulin-dependent diabetes mellitus. Patients were randomly assigned in a single-blind fashion to treatment with either lovastatin, an HMG CoA reductase inhibitor ($n = 16$; mean dose 30.0 ± 12.6 mg/day) or placebo ($n = 18$) for 2 years. Renal function was assessed by serially measuring the serum creatinine, glomerular filtration rate (using Cr^{51}-EDTA), and 24-h urinary protein excretion. Lovastatin treatment was associated with significant reductions in total cholesterol ($p < 0.001$), LDL-cholesterol ($p < 0.001$) and apo B ($p < 0.01$), the reductions at 24 months being 26, 30 and 18 %, respectively. Beneficial effects on serum triglyceride, HDL-cholesterol and apo A1 levels were also observed. Lp(a) showed no significant change in both groups. Glomerular filtration rate deteriorated significantly in the placebo group after 24 months ($p < 0.025$) but showed no significant change in the lovastatin-treated patients. The increase in serum creatinine was statistically significant ($p < 0.02$) in placebo-treated patients at 12 and 24 months, and in the lovastatin group after 24 months. Twenty-four hour urinary protein excretion increased in both groups ($p < 0.05$). Lovastatin treatment was not associated with significant elevations in liver or muscle enzymes. We conclude that effective normalisation of hypercholesterolaemia may retard the progression of diabetic nephropathy. [Diabetologia (1995) 38: 604–609]

Key words Hypercholesterolaemia, non-insulin-dependent diabetes mellitus, nephropathy, HMG CoA reductase inhibitor, lipoprotein(a), lipids, lipoproteins.

In recent years, there has been a renewed interest in the potential pathogenetic role of hyperlipidaemia in progressive glomerular injury [1], a concept first proposed over 100 years ago [2]. An increase in dietary cholesterol favours the development of glomerulosclerosis in laboratory animals [3, 4] and accelerates the progression of experimental models of uraemia and nephrotic syndrome [5, 6]. On the other hand, hypolipidaemic therapy using clofibrate or lovastatin reduces glomerular injury in these models [6, 7]. Lovastatin, an HMG CoA reductase inhibitor and a potent cholesterol-lowering agent, also ameliorates the development of glomerulosclerosis in the genetically obese Zucker rat [8], an animal model of non-insulin-dependent diabetes mellitus (NIDDM).

In diabetic nephropathy, prominent tubular, vascular and glomerular lipid deposits are found. This observation has led to the hypothesis that lipids may be important in the pathogenesis of progressive renal injury in diabetic patients, and that the promi-

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Abbreviations: NIDDM, Non-insulin-dependent diabetes mellitus; GFR, glomerular filtration rate; Lp(a), lipoprotein(a); apo, apolipoprotein; LDL, low-density lipoprotein; VLDL, very low density lipoprotein; HDL, high-density lipoprotein.

Table 1. Baseline patient characteristics

	Lovastatin	Placebo	*p*-value
Patients (*n*)	16	18	
Age (years)	58.9 ± 2.3	53.9 ± 2.5	0.15
Male : female	8 : 8	11 : 7	0.53[a]
BMI (kg/m^2)	26.0 ± 1.1	24.9 ± 0.9	0.45
Insulin therapy	9/16	10/18	0.97[a]
Smoker	4/16	3/18	0.57[a]
Fasting glucose (mmol/l)	9.4 ± 0.8	9.8 ± 0.9	0.74
HbA_{1c} (%)	7.2 ± 0.4	7.4 ± 0.5	0.77
Mean arterial pressure (mm Hg)	100.7 ± 2.1	100.8 ± 1.9	0.45
GFR (ml · min^{-1} · 1.73 m^{-2})	83.1 ± 9.5	84.3 ± 5.1	0.91
Serum creatinine (μmol/l)	93.6 ± 4.3	97.6 ± 3.1	0.46
24-h urine protein (g)	0.81 ± 0.17	1.14 ± 0.3	0.30

Mean ± SEM. Normal range for HbA_{1c}: 3.3–5.6 %
Comparison using Student's unpaired *t*-test except for [a] (Fisher's exact test)

nent mesangial expansion characteristic of established diabetic nephropathy could conceivably result from a combination of hyperlipidaemia and elevated glomerular pressure [9]. To date there has been little clinical evidence to support this hypothesis, although a relationship between hypercholesterolaemia and a more rapid decline in glomerular filtration rate in diabetic nephropathy has been previously proposed [10].

Patients with NIDDM often have multiple derangements of lipid metabolism resulting in raised levels of very low density lipoprotein (VLDL) and low-density lipoprotein (LDL), and reduced high-density lipoprotein (HDL) [11]. Lovastatin, which increases the synthesis of hepatic LDL receptors and hence fractional removal of circulating LDL and VLDL remnants [12], has been shown to be an effective hypolipidaemic agent in these patients [11]. We have investigated the long-term potential of lovastatin in the treatment of hyperlipidaemia in NIDDM patients and assessed prospectively whether the amelioration of hyperlipidaemia could confer a beneficial effect on their renal function.

Subjects and methods

Subjects. Thirty-six Chinese NIDDM patients with mild to moderate hypercholesterolaemia (fasting total cholesterol above 5.2 but less than 7.8 mmol/l) and proteinuria greater than 0.15 g/day (upper normal range of the local laboratory) were recruited into the study. All had normal serum creatinine levels (less than 120 μmol/l) and stable diabetic control (no significant change in drug dosage required during the preceding 3 months). None had experienced ketosis since the diagnosis of diabetes 2 to 20 years prior to the study. Seventeen patients were on oral hypoglycaemic agents (glibenclamide or gliclazide) with adequate glycaemic control. The other 19 patients required insulin therapy for control of hyperglycaemia but had previously been adequately controlled on oral hypoglycaemic agents alone for 5 to 12 years from diagnosis. During the study all were treated with a diet consisting of 30 kcal per kg ideal body weight, 50–55 % carbohydrate, 30 % fat, 15–20 % protein and 300 mg cholesterol which was reinforced 2 months before commencement of the study. Those taking specific hypolipidaemic drugs discontinued such therapy at least 2 months prior to the study. None had previous myocardial infarction or unstable angina or evidence of congestive heart failure, thyroid or hepatic diseases. The protocol was approved by the local Ethics Committee. Two patients withdrew from the study after 3 and 6 months, respectively – one could not attend the frequent follow-up due to a change in occupation and another emigrated. The clinical characteristics of the 34 patients who completed the 24-month study are summarised in Table 1.

Study protocol. The patients were randomly assigned by block randomization in a single-blind fashion to receive treatment with either lovastatin or placebo, while continuing with their recommended diet. Lovastatin was started at 20 mg/day given as a single evening dose, and increased by 20 mg/day at 6-week intervals if fasting total cholesterol remained above 5.2 mmol/l. The mean dosage employed was 30.0 ± 12.6 mg/day (mean ± SD; range 20–60 mg/day). All patients were assessed at the outpatient clinic basally and every 6 weeks for 1 year, then every 3 months for a further year. Dosage of drugs for the treatment of diabetes and hypertension was adjusted to maintain good glycaemic and blood pressure control. Two patients in each group were treated with atenolol; five and three patients were on nifedipine in the lovastatin and placebo group, respectively, while two and three patients respectively were on enalapril. Other antihypertensive drugs included α-methyldopa and indapamide.

At each visit, body weight and blood pressure were measured and fasting blood samples were collected for the measurement of glucose, HbA_{1c}, lipids, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, creatinine kinase and lactate dehydrogenase levels. Two 24-h urine collections were obtained initially, and subsequently every 6 months for the quantitation of protein excretion. Glomerular filtration rate (GFR) was measured using Cr^{51}-EDTA at 0, 12 and 24 months as described previously [13]. Ophthalmological examination including slit-lamp examination, fundoscopy and checking of visual acuity was performed at 0, 12 and 24 months. Visual acuity was measured tri-monthly in the interim period so that additional ophthalmological examinations could be arranged if significant deterioration occurred.

Total cholesterol and triglycerides were determined enzymatically (Boehringer Mannheim, Mannheim, Germany) on a Hitachi 717 analyser. HDL-cholesterol was measured by the same method after precipitation of VLDL and LDL with phosphotungstic acid. LDL-cholesterol was calculated according to the Friedewald equation. Apolipoproteins (apo A1 and apo B) were measured with a rate nephelometric method using the Beckman Array system (Beckman Instruments, Brea, CA, USA). Serum apolipoprotein(a) [apo(a)] was measured by immunoradiometric assay (Pharmacia, Uppsala, Sweden), the intra-assay variations at low and high apo(a) levels being 2.6 and 1.4 %, respectively. All samples from the same patient collected every 6 months were assayed for apo A1, apo B or apo(a) in the same assay. HbA_{1c} was measured by electrophor-

Table 2. Changes in blood pressure, body mass index and glycaemic control

	Mean arterial pressure (mm Hg)		BMI (kg/m^2)		HbA_{1c} (%)	
	Lovastatin	Placebo	Lovastatin	Placebo	Lovastatin	Placebo
Baseline	100.7 ± 2.1	102.8 ± 1.9	26.0 ± 1.1	24.9 ± 0.9	7.2 ± 0.4	7.4 ± 0.5
12-month	106.2 ± 3.2	104.3 ± 2.3	26.1 ± 1.1	25.5 ± 1.0	6.7 ± 0.4	6.5 ± 0.4
24-month	105.9 ± 3.2	103.4 ± 2.8	26.3 ± 1.1	25.0 ± 1.0	6.6 ± 0.4	6.8 ± 0.4

Mean ± SEM. Lovastatin, $n = 16$; placebo, $n = 18$

Table 3. Effects of lovastatin on serum lipid and lipoprotein levels in patients with diabetic nephropathy

	Total cholesterol (mmol/l)		Triglyceride (mmol/l)		HDL-cholesterol (mmol/l)		LDL-cholesterol (mmol/l)	
	Lovastatin	Placebo	Lovastatin	Placebo	Lovastatin	Placebo	Lovastatin	Placebo
Baseline	6.6 ± 0.1	6.3 ± 0.1	2.2 ± 0.3	2.9 ± 0.5	1.10 ± 0.05	1.10 ± 0.07	4.3 ± 0.3	4.1 ± 0.2
12-month	4.9 ± 0.2[c]	6.6 ± 0.2[e]	1.8 ± 0.3	3.2 ± 0.5[d]	1.07 ± 0.04	0.97 ± 0.06[b]	3.0 ± 0.2[c]	4.0 ± 0.2[e]
24-month	4.9 ± 0.1[c]	6.4 ± 0.2[e]	2.0 ± 0.4	3.7 ± 0.6[d]	1.09 ± 0.06	0.99 ± 0.07[a]	3.0 ± 0.2[c]	3.8 ± 0.2[e]

Mean ± SEM. [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.0001$; vs baseline [d] $p < 0.05$; [e] $p < 0.0001$; vs lovastatin. Lovastatin, $n = 16$; placebo, $n = 18$

Table 4. Effects of lovastatin on serum apolipoprotein levels in patients with diabetic nephropathy

	Apo A1 (g/l)		Apo B (g/l)		Apo(a) (U/l)	
	Lovastatin	Placebo	Lovastatin	Placebo	Lovastatin	Placebo
Baseline	2.01 ± 0.06	2.02 ± 0.06	1.55 ± 0.05	1.36 ± 0.05[d]	231	153
12-months	2.14 ± 0.06	2.10 ± 0.08	1.10 ± 0.06[b]	1.40 ± 0.06[d]	248	162
24-month	1.98 ± 0.08	1.90 ± 0.07	1.27 ± 0.05[a]	1.50 ± 0.07[c]	275	167

Mean ± SEM except for apo(a) [expressed as geometric mean]. Lovastatin, $n = 16$; placebo, $n = 18$. [a] $p < 0.005$; [b] $p < 0.0001$; vs baseline. [c] $p < 0.02$; [d] < 0.01; vs lovastatin.

esis using Beckman Paragon Diatrac HbA_{1c} Kit (Beckman Instruments). Urine protein was measured with a dye method (pyrogallol red) using Biotrol reagent kit (Exton, PA, USA) and a Hitachi 717 analyser (Boeringer Mannheim, GmbH, Germany). Serum creatinine was measured by the Jaffe reaction [13] on a Hitachi 737 analyser.

Statistical analysis

Statistical analyses were performed using the MINITAB (Minitab Inc., State College, Pa., USA) statistics package. Because of their skewed distribution, apo(a) levels were normalized by logarithmic transformation prior to analysis. Two-way analysis of variance was used to evaluate the serial changes during treatment. Student's *t*-test and Fisher's exact test were used for the comparison of continuous and catagoric variables, respectively.

Results

There was no significant difference between lovastatin- and placebo-treated patients in any of the clinical characteristics at baseline (Table 1), 12 months or 24 months (Table 2). Ten patients in each group required antihypertensive drugs before and during the study. In both groups, there was no significant change in mean arterial pressure, body mass index, HbA_{1c} (Table 2) or fasting blood glucose (data not shown) during the study period. Lovastatin was very well tolerated. No significant elevation in liver or muscle enzymes or increased appearance of new lens opacity was observed.

The effects of lovastatin treatment on fasting serum lipid levels are shown in Table 3. Total cholesterol and LDL-cholesterol were reduced by 26 and 30 %, respectively in the lovastatin-treated patients ($p < 0.001$; *F*-values 47.01 and 19.18, respectively), but showed no significant change in the placebo group. The changes at 12 months were sustained at 24 months. The reduction in serum triglyceride during lovastatin treatment did not reach statistical significance. On the other hand, an increasing trend in serum triglyceride was seen in the placebo-treated patients ($F = 1.78$) so that at 12 months and 24 months, serum triglyceride in the lovastatin group was significantly lower than the placebo group by 44 and 46 %, respectively ($p < 0.05$). HDL-cholesterol showed no significant change in the lovastatin group but was significantly reduced in the placebo group ($p < 0.01$, $F = 5.43$).

The changes in serum apolipoprotein levels are summarized in Table 4. A significant reduction in apo A1 was seen only in the placebo groups ($p < 0.05$, $F = 4.12$). Lovastatin treatment was associated with a significant reduction in apo B ($p < 0.001$, $F = 21$). No significant change in apo B was observed

in the placebo group. In both groups apo(a) showed no significant change during the study period.

Five patients in each group had incipient nephropathy with proteinuria of 150–500 mg/day [14,15]; all other patients had overt nephropathy with proteinuria greater than 500 mg/day. The changes in renal function are shown in Figure 1. There was no significant difference in GFR, serum creatinine or 24-h urinary protein excretion between the two groups at baseline (Table 1), 12 months or 24 months. GFR decreased in the placebo group ($p < 0.05$, $F = 3.92$) but showed no significant reduction in the lovastatin patients ($F = 0.124$). Serum creatinine increased in both lovastatin ($p < 0.05$, $F = 4.7$) and placebo ($P < 0.01$, $F = 6.9$) groups, being significantly higher than baseline levels ($p < 0.02$) at both 12 and 24 months in the placebo group, and at 24 months in the lovastatin group. Twenty-four-hour urinary protein increased in both groups during the study period ($p < 0.05$, F values 3.70 and 3.88 for lovastatin and placebo groups, respectively).

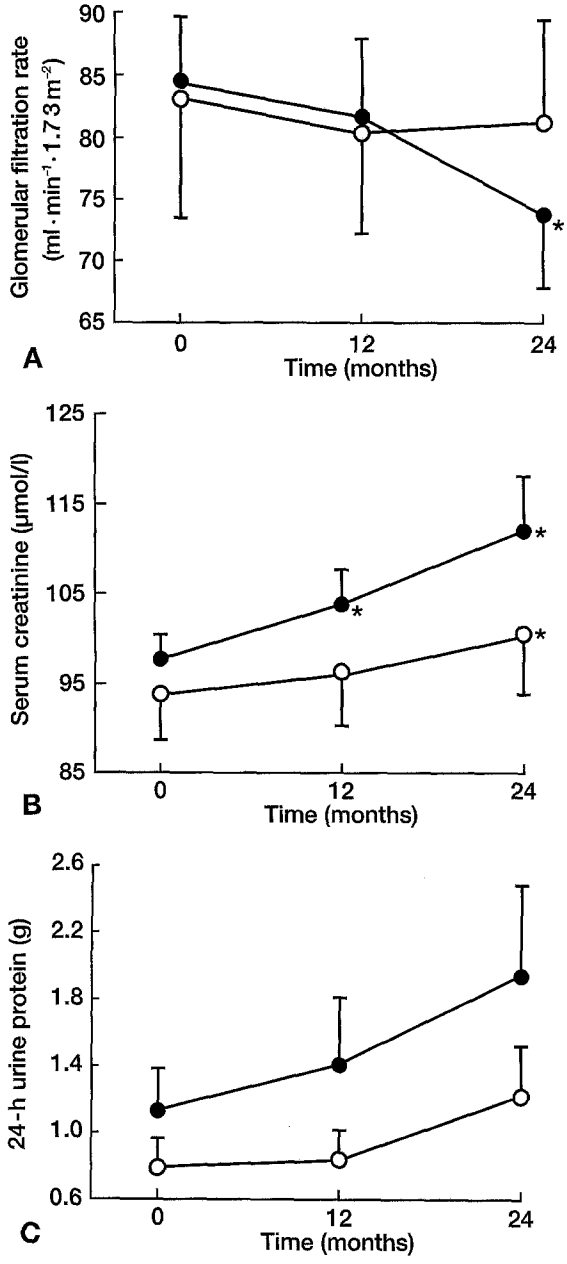

Fig. 1 (A–C). Changes in (**A**) glomerular filtration rate, (**B**) serum creatinine and (**C**) 24-h urine protein excretion in patients treated with lovastatin (o----o; $n = 16$) or placebo (●----●; $n = 18$); * $p < 0.025$ vs pre-treatment

Discussion

In this 2-year prospective study, we found that long-term normalisation of hypercholesterolaemia appeared to have a beneficial effect on the renal function of NIDDM patients with hyperlipidaemia. While GFR progressively declined in the placebo group, an apparent retardation in the fall in GFR was observed in the patients treated with lovastatin. The changes in serum creatinine were also in keeping with an attenuating effect of lovastatin on the deterioration of glomerular function in these patients. A beneficial effect of lovastatin on GFR in Chinese patients with non-diabetic nephrotic syndrome has been previously reported [13]. The course of proteinuria was not affected by long-term lovastatin treatment, in contrast to the reduction in albuminuria following treatment with pravastatin, another HMG CoA reductase inhibitor, reported in an open 12-week study involving nine Japanese patients with diabetic nephropathy [16]. Although proteinuria is a good prognostic index of progressive renal disease in early stages of nephropathy, urinary protein excretion rate may fall when the GFR becomes significantly reduced so that it becomes less reliable as an index of progressive renal disease.

In experimental animals there is ample evidence that hypercholesterolaemia, either spontaneous [8] or induced [3–5], is associated with the development of progressive glomerular injury, which can be ameliorated by hypolipidaemic therapy [6–8]. The rare condition of lecithin cholesterol acyltransferase (LCAT) deficiency also represents an example in man of progressive renal injury occurring as a result of abnormal lipoprotein metabolism [1]. In this disease which is characterised by an abnormal serum LDL-fraction, a link between the abnormal LDL and renal injury has been inferred [17]. The mechanism by which hypercholesterolaemia causes or aggravates glomerular injury is not known. Specific binding and uptake of LDL has been demonstrated in rat mesangial cells [18]. In human nephritic kidneys, glomerular epithelial and mesangial cells have been shown to express both LDL receptors and scavenger receptors [19]. Furthermore, in glomeruli showing marked mesangial proliferation, glomerular expression of scavenger receptors was increased.

It has therefore been postulated that the accumulation of apo B and apo E, whether mediated by receptors or other mechanisms, may be associated with mesangial expansion [19]. An increase in renal cortical tissue cholesterol ester content has also been noted in hypercholesterolaemic rats [20]. Under physiological conditions, VLDL and LDL can bind with polyanionic glycosaminoglycans [21]. Binding of increased circulating low-density lipoproteins with glycosaminoglycans in the glomerular basement membrane will increase its permeability and hence increase protein loss. Injury of glomerular basement membrane may also result in the accumulation of filtered lipoproteins in the mesangial cells, leading to mesangial expansion and excess basement membrane production [1]. In the diabetic kidney, it has been shown that the decline in GFR is caused by a reduction in glomerular filtration surface area due to mesangial expansion [22]. The marked reduction in circulating LDL in our NIDDM patients may retard the decline in GFR by removing one of the stimuli for mesangial expansion.

In these patients with moderately severe NIDDM, impaired lipoprotein lipase activity [23] can lead to the accumulation of VLDL and VLDL remnants while reduced catabolism [24] of modified LDL can lead to raised LDL levels. These lipoprotein abnormalities tend to occur more commonly in the presence of nephropathy [25], perhaps because of the urinary loss of lipoprotein lipase activators [26]. Thus, in our placebo-treated patients, serum triglyceride levels tended to increase with progressive renal injury. The satisfactory reductions in total cholesterol, LDL-cholesterol and apo B levels observed in our lovastatin-treated patients are in keeping with observations in Caucasian patients with NIDDM and hyperlipidaemia [11]. An increase in Lp(a) levels was previously reported in non-diabetic patients after 9 months of lovastatin therapy [27]. In our patients treated with lovastatin, no significant increase in plasma apo(a) and, by implication, of Lp(a) was observed during the 24-month study period, in agreement with the findings of a short-term study in Chinese patients with uraemia [28]. Lovastatin also appears to have a beneficial effect on serum triglyceride and HDL-cholesterol in these patients with diabetic nephropathy. In agreement with observations in Caucasian patients [11, 29], lovastatin appears to be a safe drug for the long-term treatment of these Chinese diabetic patients with hypercholesterolaemia, even in the presence of mild renal impairment.

Patients with diabetic nephropathy tend to run a progressive downhill course. The progression can be delayed by antihypertensive therapy [30], and may be influenced by the quality of metabolic control [31] and protein intake [32]. Recently, an association of smoking with the progression of diabetic nephropathy has also been suggested [33]. The findings of this small study are supportive of a pathogenetic role of hypercholesterolaemia in progressive diabetic glomerular disease. The full potential of cholesterol-lowering therapy as an additional means to retard the progression of diabetic nephropathy remains to be established in longer-term studies involving a larger number of patients.

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References

1. Moorhead JF, EL Nahas M, Chan MK, Varghese I (1982) Lipid nephrotoxicity in chronic progressive glomerular and tubulo-interstitial disease. Lancet 2: 1309–1310
2. Virchow R (1860) A more precise account of fatty metamorphosis. In: Chance F (ed) Cellular pathology 2nd edn. Gryphonham, Gryphon Editions, pp 342–366
3. French SW, Yamanaka W, Ostward R (1967) Dietary induced glomerulosclerosis in the guinea pig. Arch Pathol 83: 204–210
4. Wellmann K, Volk BW (1970) Renal changes in experimental hypercholesterolaemia in normal and in subdiabetic rabbits. Lab Invest 22: 144–155
5. Diamond JR, Karnovsky MJ (1987) Exacerbation of chronic aminonucleotide nephrosis by dietary cholesterol supplementation. Kidney Int 32: 671–678
6. Kasiske BL, O'Donnell MP, Garvis WJ, Keane WF (1988) Pharmacologic treatment of hyperlipidaemia reduces glomerular injury in rat 5/6 nephrectomy model of chronic renal failure. Circulation Res 62: 267–274
7. Harris KPG, Purkerson ML, Yates J, Klahr S (1990) Lovastatin ameliorates the development of glomerulosclerosis and uraemia in experimental nephrotic syndrome. Am J Kidney Dis 15: 16–23
8. Kasiske BL, O'Donnell MP, Cleary MP, Keane WF (1988) Treatment of hyperlipidaemia reduces glomerular injury in obese Zucker rats. Kidney Int 33: 667–672
9. Wilens SL, Elster SK (1951) The role of lipid deposition in renal arteriolar sclerosis. Am J Med Sci 219: 183–196
10. Mulec H, Johnson S-A, Bjorck S (1990) Relation between serum cholesterol and diabetic nephropathy. Lancet 335: 1537–1538
11. Garg A, Grundy SM (1988) Lovastatin for lowering cholesterol level in non-insulin-dependent diabetes mellitus. N Engl J Med 318: 81–86
12. Bilheimer DW, Grundy SM, Brown MS, Goldstein JL (1983) Mevinolin and colestipol stimulate receptor mediated clearance of low density lipoprotein from plasma in familial hypercholesterolaemia heterozygotes. Proc Natl Acad Sci USA 80: 4124–4128
13. Chan PCK, Robinson JD, Yang WC, Cheng IKP, Yeung HWD, Tsang MTS (1992) Lovastatin in glomerulonephritis patients with hyperlipidaemia and heavy proteinuria. Nephrol Dial Transplant 7: 93–99
14. Sawicki PT, Heinemann L, Berger M (1989) Comparison of methods for determination of microalbuminuria in diabetic patients. Diabet Med 6: 412–415

15. Mogensen CE, Christensen CK, Vittinghus E (1983) The stages in diabetic renal disease: with emphasis on the stage of incipient diabetic nephropathy. Diabetes 32 (Suppl 2): 64–78
16. Sasak T, Kurata H, Nomura K, Utsunomiya K, Ikeda Y (1990) Amelioration of proteinuria with pravastatin in hypercholesterolaemic patients with diabetes mellitus. Jpn J Med 29: 156–163
17. Gione E, Bloomhoff JP, Skarbovik AJ (1970) Possible association between an abnormal lipoprotein and nephropathy in lecithin: cholesterol acyltransferase deficiency. Clin Chim Acta 54: 11–18
18. Wasserman J, Santiago A, Holthofer H, Epstein M, Schlondoreq D (1989) Interactions of low density lipoprotein with rat mesangial cells. Kidney Int 35: 1168–1174
19. Takemura T, Yoshioka K, Aya N, Murakami K, Matsumoto A, Itakura H (1993) Apolipoproteins and lipoprotein receptor in glomeruli in human kidney diseases. Kidney Int 43: 918–927
20. Peric-Golia L, Peric-Golia M (1983) Aortic and renal lesions in hypercholesterolaemic adult male, virgin Sprague-Dawley rats. Atherosclerosis 46: 57–65
21. Iverius PH (1972) The interaction between human plasma lipoproteins and connective tissue glycosaminoglycans. J Biol Chem 247: 2607–2613
22. Ellis EN, Steffes MW, Goetz FC, Sutherland DER, Mauer SM (1986) Glomerular filtration surface in type 1 diabetes mellitus. Kidney Int 29: 889–894
23. Taskinen MR, Nikkila EA, Kussi T, Harno K (1982) Lipoprotein lipase activity and serum lipoproteins in untreated type 2 diabetes associated with obesity. Diabetologia 22: 46–50
24. Steinbrecher UP, Witztum JL (1984) Glucosylation of low-density lipoproteins to an extent comparable to that seen in diabetes slows their catabolism. Diabetes 33: 130–134
25. Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR (1991) Effect of restricting dietary protein on the progression of renal failure in patients with insulin dependent diabetes mellitus. New Engl J Med 324:78–84
26. De Mendoza SG, Kashyap ML, Chen CY, Lutmer RF (1976) High density lipoproteinuria in nephrotic syndrome. Metabolism 25: 1143–1149
27. Kostner GM, Gavish D, Leopold B, Bolzano K, Weintraub MS, Breslow JL (1989) HMG CoA reductase inhibitors lower LDL-cholesterol without reducing Lp(a) levels. Circulation 80: 1313–1319
28. Li PKT, Mak TWL, Chiu K et al. (1993) Effect of lovastatin on serum lipid profile in the treatment of dyslipoproteinaemia in uraemic patients on continuous ambulatory peritoneal dialysis. Aust NZ J Med 23: 252–257
29. Tobert JA (1987) New developments in lipid-lowering therapy: the role of inhibitors of hydroxymethylglutaryl coenzyme A reductase. Circulation 76: 534–538
30. Mogensen CE (1982) Long-term antihypertensive treatment inhibiting progression of diabetes nephropathy. BMJ 85: 685–688
31. Feld-Rasmussen B, Mathiesen ER, Lensen T, Lauritzen T, Deckert T (1991) Effect of improved metabolic control on loss of kidney function in type 1 (insulin-dependent) diabetes patients – an update of the Steno studies. Diabetologia 34: 164–170
32. Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR (1991) Effect of resticting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. N Engl J Med 324: 78–84
33. Sawicki PT, Didjurgeit U, Muhlhauser I, Bende R, Heinemann L, Berger M (1994) Smoking is associated with progression of diabetes nephropathy. Diabetes Care 17: 126–131