Kidney International, Vol. 21 (1982), pp. 730–738

The kidney in maturity onset diabetes mellitus: A clinical study of 510 patients

JEAN FABRE, LUC P. BALANT, PIERRE G. DAYER, HILKE M. FOX, and ANDRÉ T. VERNET

Policlinique de médecine, Department of Medicine, University of Geneva, Geneva, Switzerland

Nephropathy associated with type 1 (insulin-dependent, juvenile onset) or type 2 (noninsulin-dependent, maturity onset) diabetes mellitus is histologically characterized by glomerulosclerosis, hyalinosis of afferent and efferent glomerular arterioles and sometimes pyelonephritis [1–5]. Because diabetic nephropathy with renal failure is considered the cause of death in 42% of the patients below age 20 at the onset of diabetes mellitus, 9% between ages 20 and 39 but only 2.5 or 0.8% between ages 40 and 59 or beyond age 60, respectively [2], it is not surprising that interest in the clinical manifestations and pathophysiology of this complication has centered almost exclusively on type 1, insulin-dependent, juvenile onset diabetes mellitus [6–8].

However, type 2 diabetes mellitus is the most prevalent form of the syndrome, occurring principally after age 40, noninsulin-dependent, without a tendency to ketoacidosis and frequently associated with obesity.

Indeed 80% of all diabetic patients show their first symptoms after age 40. Accordingly, this study investigated the clinical manifestations of renal disease in a large number of patients with maturity onset diabetes mellitus. Emphasis in this study was placed on hypertension, frequently observed in these patients, and on quantitative as well as qualitative protein excretion, which provide a useful marker of glomerular or tubule dysfunction when analyzed according to the molecular weight of the various fractions excreted. In this way, the course of renal involvement in maturity onset diabetes mellitus has been assessed and quantified. The results revealed an evolution which is quite different from that seen in juvenile onset, insulin-dependent diabetes mellitus.

Methods

Patients. This report involved 510 diabetic patients diagnosed after age 40, characterized by fasting blood glucose between 160 and 1840 mg/dl (8.9 and 102 mmoles/liter) at the time of the diagnosis and the absence of ketoacidosis. They were chosen randomly and represent 85% of the diabetic patients coming to the Policlinique de médecine outpatient clinic. The group comprised 345 women and 165 men, aged between 42 and 92. After age 65, female predominence in the group was striking (Fig. 1). For reasons linked to the organization of social security, these figures are not quite representative of the general population suffering from maturity onset diabetes mellitus. The apparent duration of diabetes mellitus ranged from a few months to 35 years (Table 1). Most of the patients were followed for years, with controls every 1 to 3 months. Two-thirds were obese, in excess of the ideal weight by 20% according to the Lorenz formula:

$$\text{ideal weight (kg)} = \text{height (cm)} - 100 - (\text{height} - 150) \div 4.$$

Angina pectoris or history of myocardial infarction were found in 15% of the patients, intermittent claudication or gangrene in 4%, history of cerebral vascular accident in 4%, diabetic retinopathy grade 2 to 4 in 49%. Eighty-seven patients received digoxin and/or diuretics for heart failure, which was generally well controlled.

Arterial hypertension was clearly established in 236 patients with casual diastolic readings (point of disappearance of the arterial sounds) of 110 mm Hg or more on several visits; in most of the patients, it was totally or partially corrected by antihypertensive drugs when the renal tests were performed. A further 167 patients had mild hypertension with several diastolic readings between 95 and 109 mm Hg. The BP was measured in the supine position after at least 10 min of rest. A long (18 × 88 cm) cuff with a 17 × 28 cm inflatable bladder was generally used in obese patients.

Histopathological examination of renal tissue was available from biopsy or autopsy specimens in 50 patients. Seven patients had histopathological signs, beyond glomerulosclerosis with hyalinosis of the afferent and efferent glomerular arterioles, of interstitial nephritis suggestive of pyelonephritis; two had proliferative glomerulonephritis, and one had congenital nephropathy.

Treatment of diabetes mellitus. One hundred and fourteen patients were on a diabetic diet without added agents and 231 on a diet plus oral agents (sulfonylureas and/or metformine). In 165 patients, insulin treatment was given for control of blood glucose but not for ketoacidosis; consequently, most of the patients were considered, nevertheless, to be noninsulin-dependent.

Evaluation of diabetic control. Control was considered to be "satisfactory" when blood glucose (1 to 2 hr postprandial or, less often, fasting) did not exceed 200 mg/dl (11 mmoles/liter, allowance for one reading out of ten in excess of these values was made). With several blood glucose measurements between 200 and 300 mg/dl (16.7 mmoles/liter), control was considered to

Received for publication November 18, 1981
0085–2538/82/0021–0730 $01.80

Table 1. Effect of duration of diabetes mellitus on protein excretion ($P = 0.003$)[a]

Duration of diabetes mellitus	N	Protein excretion, *mg/24 hr*			
		0 to 79	80 to 149	150 to 499	⩾500
0 to 1 yr	84 (100%)	29%	34%	32%	5%
2 to 5 yr	122 (100%)	29%	24%	38%	9%
6 to 10 yr	108 (100%)	32%	23%	29%	16%
11 to 15 yr	86 (100%)	27%	23%	29%	21%
16 to 20 yr	53 (100%)	19%	23%	32%	26%
>20 yr	37 (100%)	27%	16%	22%	35%

[a] Percentage given indicates distribution for each duration of diabetes mellitus. Based on data obtained for 490 diabetic patients. In 20 cases, onset of diabetes mellitus was difficult to assess.

be "fair". Whenever it exceeded 300 mg/dl at times, it was labelled as "poor".

Nondiabetic control persons. Renal investigations were carried out in 87 healthy nondiabetic control persons with normal BP, negative sulfosalicylic acid test, normal urinary sediment, and no history of kidney disease. They were sex- and age-matched with diabetes mellitus patients (40 to 85 years).

Renal investigations

The 510 diabetes mellitus patients and the 87 nondiabetic control persons underwent the following set of investigations:

(1) Dosage of urinary proteins. Urine samples were collected separately in the day (patients moved around freely but were not subjected to any heavy effort), and at night (in strict recumbency). Sodium azide was used for conservation. Proteins were determined on the two samples by a modification of the biuret method, utilizing precipitation by phosphotungstic acid in 45% ethanol [9].

(2) Electrophoresis of the urinary proteins. Electrophoreses were performed on night-time urine samples to avoid changes in the relative amount of various urinary proteins by upright position and effort [10]. The urine samples were concentrated by ultrafiltration on Amicon UM-10 membranes under a pressure of nitrogen, followed by further concentration on Minicon or, before 1974, by dialysis against polyethylene glycol at 4° [11].

Cellulose acetate electrophoresis (Beckman Microzone System, strips stained with Ponceau red) and immuno-electrophoresis according to the micromethod described by Scheidegger [12] were performed on urine concentrate.

In 269 patients observed after 1974, these methods were completed by polyacrylamide gel electrophoresis after treatment by sodium dodecylsulfate (SDS electrophoresis) according to Balant, Mulli, and Fabre [13]. This detergent caused the proteins to form negatively charged protein-SDS micelles. When subjected to electrophoresis, these micelles migrated a distance correlating well with the molecular weight of the protein without the influence of its electrostatic charge. Measurement of the peak surfaces with an integrator gave the percentage of the proteins: proteins of high molecular weight (HMW), above 100,000; middle molecular weight (MMW), between 50,000 and 100,000; and low molecular weight (LMW), under 50,000. The proportion of albumin, an important MMW component, was also measured. The excretion rate of the HMW, MMW, LMW, and albumin was calculated in μg/min from the quantity of proteins excreted per minute in recumbency during the night.

The electrophoresis allowed a distinction between physiological, glomerular, tubular, and mixed patterns of proteinuria, according to criteria described elsewhere [14–16]. The major advantage of SDS electrophoresis is an objective determination of these patterns, established by a nomogram according to the percentage of different molecular weight groups: predominantly MMW and HMW proteins in glomerular patterns, mostly LMW in tubular patterns [16]. The three methods used gave the same results in 95% of the patients. In case of discrepancy, the result of the SDS electrophoresis was taken in account.

(3) Measurement of the urinary lysozyme [17].

(4) Determination of the GFR was made in fasting and recumbent patients by studying the plasma disappearance of ^{51}Cr-EDTA after a single intravenous injection [18] and by measuring the clearance of creatinine on a 2-hr urine sample.

(5) Urinary sediment and cell count were taken according to Hamburger, Mathé, and de Vergizier [19].

(6) A semi-quantitative count of micro-organisms was made in urine samples (Uricult®).

Investigations *(1)* through *(6)* were undertaken on the same day for a given patient. In a few cases, some tests were not carried out for technical or practical reasons, as will be specified in the section describing results.

Statistical analysis. The data of each table were analyzed by standard χ^2 test with or without Yate's correction and, when necessary, after splitting of the χ^2. General correlations were examined with a log-linear model (discrete multivariate analysis [20]).

Results

Urinary excretion of proteins

Total protein excretion. Of 510 patients with maturity onset diabetes mellitus, 48% had protein excretion above 150 mg/24 hr, a level never reached in the nondiabetic control persons. Eighty-one patients showed proteinuria in excess of 500 mg/24 hr, 18 only exceeded 3,000 mg/24 hr, including nine with a complete nephrotic syndrome (Fig. 2).

By contrast, the mean protein excretion of 87 nondiabetic controls was 50 mg/24 hr (8 to 133 mg/24 hr); in 81% of these it was below 80 mg/24 hr. Even the 264 diabetes mellitus patients with normal protein excretion (less than 150 mg/24 hr) differed from control persons, as a group, because their mean excretion

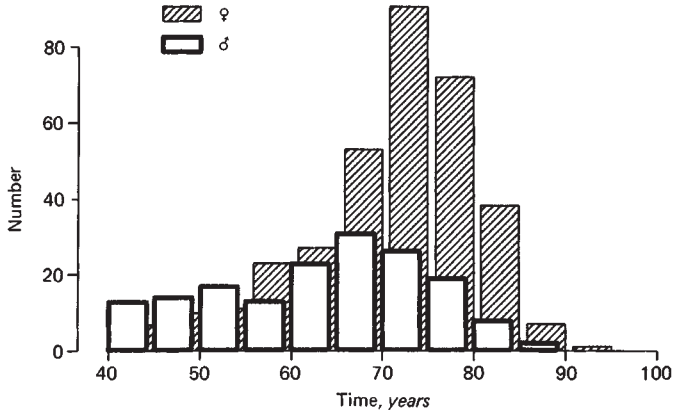

Fig. 1. *Age distribution of 510 diabetes mellitus patients (345 women, 165 men).*

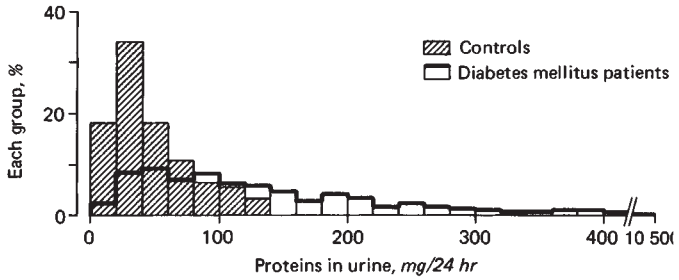

Fig. 2. *Distribution of 24-hr urinary excretion rate of proteins among 510 diabetes mellitus patients and 87 matched nondiabetic control persons, indicated as percentage of each group ($P < 0.001$).* In 20.1% of patients with diabetes mellitus, proteinuria exceeded 500 mg/24 hr. The highest excretion noted was 10 500 mg/24 hr.

was 77 mg/24 hr (2 to 150 mg/24 hr); only 53% were below 80 mg/24 hr.

Upright position, as compared to recumbency, increased the excretion of proteins in control persons (Table 2). This change was reduced in diabetes mellitus patients. No increase of the mean excretion during the day study as compared with the night study was observed in diabetes mellitus patients with values above 150 mg/24 hr.

Sex and age did not significantly affect protein excretion during recumbency in controls (27.3 μg/min in women, 24.3 μg/min in men; 24.5 μg/min between ages 40 and 60, 29.9 μg/min between ages 60 and 85). Among diabetes mellitus patients, this excretion was higher in women and older patients, but that may be explained by other factors, such as the duration of diabetes mellitus or hypertension, as will be seen below.

Urinary protein excretion according to nature and molecular weight (Fig. 3 and Table 3). Among nondiabetic control persons, urinary excretion of albumin ranged from 2 to 9 μg/min in 69%, and in 95% it was less than 24 μg/min. Of the 469 diabetes mellitus patients whose excretion rate of albumin was measured, 167 (36%) excreted only less than 24 μg/min, whereas 46 (9.8%) showed excretion in excess of 500 μg/min.

The HMW excretion was below 12 μg/min in 95% of the control persons, but it was below that level in only 51% of the 269 diabetes mellitus patients who were studied by SDS electrophoresis.

In control persons, 95% of the excretion rates of LMW were below 24 μg/min as compared to 54% in diabetes mellitus patients.

The urinary excretion of lysozyme, a LMW protein with a molecular weight of 15,000, was measured in 380 patients (normal up to 2 μg/min). It was between 3 and 18 μg/min in 95 patients. Of the latter, 35 patients had urinary infection at the time of investigation (as defined by the presence of 10^5 microorganisms/ml), a proportion higher than in the patients with normal lysozymuria ($P < 0.001$). There was no significant correlation between lysozyme and protein excretions.

Electrophoretic patterns (Table 3). Increased excretion of albumin and HMW proteins tended to produce a glomerular pattern in the electrophoresis of urinary proteins of diabetes mellitus patients. This pattern applied to all patients with proteinuria in excess of 500 mg/24 hr except for 20 patients in whom simultaneous excretion of large amounts of LMW proteins produced a mixed pattern. Of the 463 diabetes mellitus patients who were studied by electrophoresis, the pattern was glomerular in 27%, tubular in 3%, and mixed in 6%.

Among the patients with the tubular pattern, characterized by marked excretion of LMW proteins, 85% had a history of past urinary infection and often clinical and radiological manifestations compatible with pyelonephritis. It should be noted, however, that pyelonephritis can also produce glomerular or mixed patterns.

First changes in repartition of urinary proteins in diabetes mellitus patients. Of 264 diabetes mellitus patients with normal quantitative protein excretion (less than 150 mg/24 hr), 36% already showed one or several qualitative abnormalities in the excretion of proteins in recumbency: albumin, HMW and/or LMW proteins exceeding the values found in 99% of controls, and/or glomerular, tubular, or mixed electrophoretic pattern (Table 3). Of the control persons matched for age and sex, only 3% had one or several of these abnormalities.

Application of less restrictive criteria, for example, inclusion of glomerular and tubular trends and/or excretion of albumin, HMW and LMW proteins in excess of that noted for 95% of controls, showed that 66% of the diabetes mellitus patients were affected as compared to 25% of the control persons.

GFR

In 489 diabetic patients GFR was estimated, generally by the more accurate ^{51}Cr-EDTA method or, in 32 cases, by determination of clearance of creatinine only. The GFR was considered to be normal for the age of these patients (above 80 ml/min/1.73 m^2) in 83% of diabetes mellitus patients with protein excretion below 150 mg/24 hr and in only 65% of patients with excretion above this value ($P < 0.001$). There were only 43 patients (8.7%) with a GFR below 60 ml/min. The only patient of this study's series who had to be dialyzed was suffering from proliferative glomerulonephritis in addition to diabetic nephropathy. With the exception of this patient, none of the diabetes mellitus patients died of renal failure, whereas 121 were known to be deceased from other causes 1 to 8 years after this study's investigations, chiefly from coronary heart disease.

Table 2. Protein excretion during the night (strict recumbency) and during the day (frequent upright position): Mean (range)[a]

	Protein excretion			N increasing[b]/ *N in the group*
	In 24 hr *mg/24 hr*	Night-time *μg/min*	Day-time *μg/min*	
Nondiabetic control persons	50 (8 to 133)	27 (4 to 95)	40 (6 to 126)	*59/87* (68%)
Diabetes mellitus patients				
Protein excretion < 150 *mg/24 hr*	77 (4 to 149)	46 (3 to 125)	54 (3 to 144)	*147/264* (56%)
Protein excretion 150 to 499 *mg/24 hr*	282 (150 to 499)	197 (39 to 590)	196 (48 to 469)	*77/165* (47%)
Protein excretion ≥ 500 *mg/24 hr*	1800 (500 to 10050)	1234 (220 to 7544)	1248 (330 to 5238)	*27/81* (33%)

[a] Reduced effect of upright position as protein excretion increases ($P = 0.001$).
[b] Number of patients increasing their proteinuria by 25% or more in the day-time collection as compared to the night-time collection.

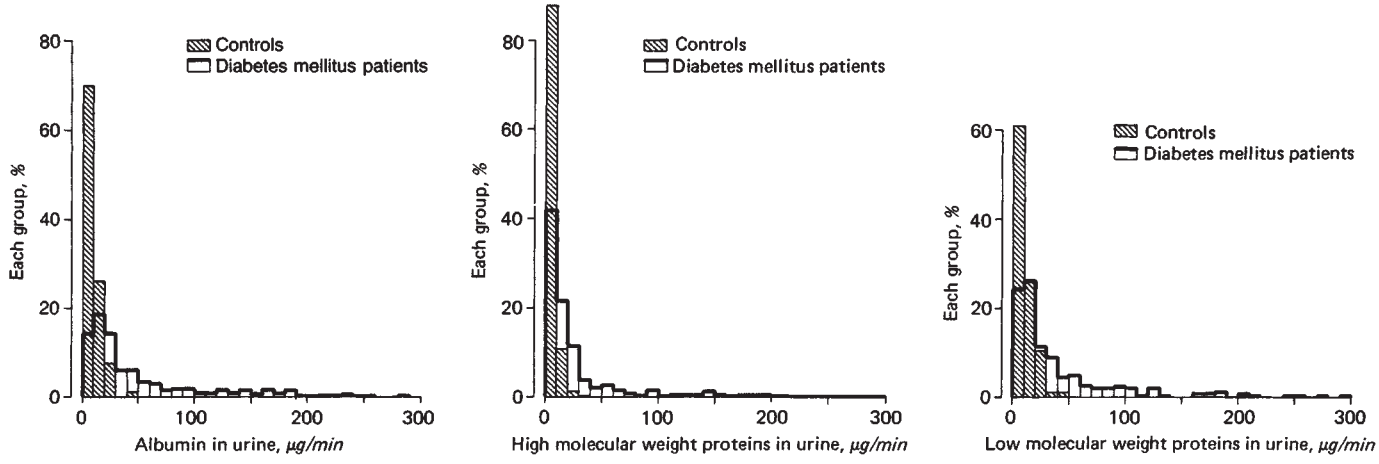

Fig. 3. *Distribution of urinary excretion rate of albumin in 463 diabetes mellitus patients* (left panel), *HMW proteins* (middle panel), *and LMW proteins* (right panel) *in 269 diabetes mellitus patients with SDS electrophoresis, as compared to 87 controls ($P < 0.001$ for each).* Percentages indicate distribution within each group. Albumin excretion rate exceeded 300 μg/min in 13% of the diabetes mellitus patients, MMW proteins in 4.7%, and LMW in 4.6%.

Urinary cells and micro-organisms

Hematuria was in excess of 5,000 red cells/min in 89 patients and of 50,000 only in an additional 13 patients. There is a correlation with protein excretion ($P < 0.005$).

Leucocyturia between 5,000 and 50,000 white cells/min was found in 117 cases and above 50,000 in 37 cases.

At the time of investigations, bacteriuria with 10^5 or more micro-organisms/ml were found in 19% of the mostly women patients.

BP

Of 510 diabetes mellitus patients, 46% had clearly established diastolic arterial hypertension (Table 4). As shown in Figure 4, hypertension was observed more frequently in women than in men inside the age groups, especially after age 70. Twenty-seven patients had systolic BP exceeding 170 mm Hg with diastolic readings constantly below 95 mm Hg, thus presenting pure systolic hypertension.

There was a correlation between arterial hypertension and increased protein excretion and especially with the fall of GFR (Table 4). Only 4% of the normotensive patients had a GFR of less than 60 ml/min as compared with 14% of the hypertensive patients.

Of the 236 hypertensive diabetic patients, 26% were hypertensive 2 to 35 years prior to the diagnosis of diabetes mellitus whereas 40% developed hypertension 2 to 29 years after diagnosis. In 34% the two findings were noted simultaneously [21]. Changes in GFR were comparable regardless of whether hypertension preceeded or followed diabetes mellitus (GFR < 60 ml/min in 12% and 14%, respectively). Proteinuria exceeding 500 mg/24 hr was noted more frequently in patients who were diabetic before they became hypertensive (21%) than vice versa (14%, $P < 0.01$).

Effect of glycemic control

The control of blood glucose was correlated inversely with protein excretion (Table 5).

Protein excretion was more frequently above 500 mg/24 hr and less frequently below 80 or 150 mg/24 hr in patients receiving insulin than in other diabetics ($P < 0.03$). But the latter were, in the mean, older patients and had a higher blood glucose concentration.

Effect of duration of diabetes

Of 84 patients studied less than one year after the diagnosis of diabetes mellitus, 37% had protein excretion above 150 mg/24 hr, and a further 24% with protein excretion in the normal range

Table 3. Excretion rate of albumin, HMW, and LMW proteins, and electrophoretic patterns of urinary proteins

	Control persons	Diabetes mellitus patients		
		Protein excretion		
		<150 mg/24 hr	*≥150 mg/24 hr*	All
Number of patients	*87*	*215*	*248*	*463*
Individual fractions				
Albumin ≥ 24 μg/min[e]	5%	30%	96%	64%
High MW[a] ≥ 12 μg/min[e]	5%	21%	92%	49%
Low MW[a] ≥ 24 μg/min[e]	5%	18%	85%	46%
Electrophoretic pattern				
Physiologic[e]	79%	68%	25%	45%
Glomerular trend	10%	11%	13%	12%
Tubular trend[e]	10%	13%	2%	7%
Glomerular[e]	1%	7%	44%	27%
Tubular	0	1%	4%	3%
Mixed[e]	0	0	12%	6%
Cumulative abnormalities				
One or more obvious abnormalities[b,e]	3%	36%	71%[d]	55%
Any kind of abnormality[c,e]	25%	66%	77%[d]	72%

[a] Results are based on findings obtained for 87 nondiabetic control persons and 269 diabetes mellitus patients who had a SDS electrophoresis.
[b] Glomerular, tubular, or mixed patterns and/or excretion rate of albumin, HMW, and LMW proteins above the upper limit reached by 99% of controls.
[c] Same patients as described under [b] plus glomerular or tubular trends and/or excretion rate of albumin and/or HMW and LMW proteins above the upper limit reached by 95% of controls.
[d] Of 52 patients with protein excretion in excess of 150 mg/24 hr but without other abnormalities, 27 patients had no SDS electrophoresis; HMW and LMW fractions were consequently not determined. This accounts for an underestimation of possible abnormalities.
[e] $P < 0.001$
Abbreviations are HMW, high molecular weight; LMW, low molecular weight.

Table 4. Relation between level of diastolic BP and protein excretion (below and above 150 mg/24 hr: $P = 0.027$) as well as GFR ($P = 0.001$)[a]

Diastolic BP before anti-hypertensive treatment	Protein excretion, *mg/24 hr*					GFR, *ml/min/1.73 m²*			
	N	0 to 79	80 to 149	150 to 499	>500	*N*	80	79 to 60	<60
Always <95 *mm Hg*	107 (100%)	38%	27%	23%	12%	106 (100%)	86%	10%	4%
Intermediate	167 (100%)	29%	23%	32%	16%	161 (100%)	75%	17%	8%
Several >110 *mm Hg*	236 (100%)	24%	28%	30%	18%	222 (100%)	63%	23%	14%

[a] Percentage of patients within each blood pressure group; *N* represents number of patients.

had albumin of HMW proteins exceeding the values found in 99% of the controls and/or glomerular electrophoretic pattern. It is likely that most of them already had metabolic disturbances for a longer time before the diagnosis.

With the duration of diabetes mellitus, proteinuria in excess of 500 mg/24 hr was found more frequently (Table 1). It is striking to note, however, that one diabetes mellitus patient out of two continued to have strictly normal protein excretion regardless of duration.

Among 90 patients with known diabetes mellitus of at least 16 years' duration, 38 had protein excretion of less than 150 mg/24 hr and frequently far below this figure. In this fortunate group, 29 patients had a GFR above 80 ml/min; 16 had been diabetic for over 20 years.

Discussion

It is beyond the scope of this paper to analyze in detail all of the observations made in this group of 510 diabetes mellitus patients. Quite generally, it is considered that the major findings all relate to a central, and in itself, paradoxical fact: Abnormal protein excretion in maturity onset diabetes mellitus occurs quite as frequently and sooner as in juvenile onset diabetes mellitus, but the characteristics, severity, and outcome of the nephropathy differ to a major and surprising extent.

Protein excretion. Half of the patients had abnormal protein excretion, and often early on in the course of their illness. In the remaining patients, there was a clear-cut tendency for the values noted to be greater than those of the age-matched nondiabetic control persons. This finding also applied to albumin excretion, which exceeded that of control persons in nearly one third of the diabetic patients with normal quantitative protein excretion. These patients, therefore, differ from the juvenile insulin-dependent diabetic patients studied by Mogensen in as far as the latter retained normal albumine excretion over a much longer period of time [7, 22]. Other studies that also contrast with Mogensen's findings and show results that

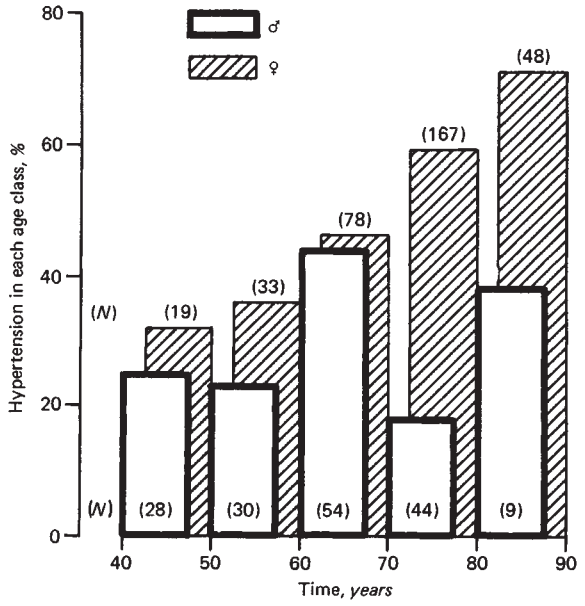

Fig. 4. *Age distribution of diabetes mellitus patients with diastolic arterial hypertension of 110 mm Hg or more before anti-hypertensive treatment.* The difference between sexes is significant ($P < 0.001$).

are close to those reported here, concerned patients of all age groups and included a sizeable number of cases with maturity onset diabetes mellitus [23–25].

Excessive urinary excretion of HMW proteins (greater than 100,000) and albumin also was noted frequently. It was sometimes the only abnormal finding and may thus be considered to be the first laboratory indicator of renal involvement in diabetes mellitus. Because SDS electrophoresis provided an easy method of distinguishing proteins according to their molecular weight, it was a useful tool in the early detection and long term follow-up of diabetic nephropathy [26–28]. Determination of low molecular weight proteins in the urine allowed a useful index of tubule involvement.

Interpretation of renal abnormalities in maturity onset diabetes mellitus is difficult because of superimposed age-dependent factors [29]. Therefore, a criteria of normality was established by matching diabetic patients with control persons according to age. Only 33% of the diabetic patients studied had perfectly normal quantitative and qualitative protein excretion, compared to 97% of the age-matched nondiabetic control persons. The difference between the diabetic and control groups was not only glucose intolerance in the former, but the whole set of abnormalities associated frequently with maturity onset diabetes mellitus, such as cardiovascular complications and hypertension.

Causes of proteinuria. It is difficult to distinguish clearly between different aspects of intricate morphological and functional changes in the pathophysiology of proteinuria in diabetes mellitus [3–8], a problem which is magnified further in older patients with cardiovascular complications: The complexity of the renal involvement in maturity onset diabetes mellitus is disheartening and explains the lack of precise data in this field.

All of the 50 patients who had a histopathological examination of renal tissue exhibited diffuse or nodular glomerulosclerosis and arteriolar hyalinosis. Although these lesions are likely to induce alterations in renal function, it has been shown that they may be quite extensive without necessarily leading to proteinuria [1, 2, 30].

Table 5. Protein excretion according to the quality of diabetic control ($P = 0.001$)[a]

Control	*N*	Protein excretion, *mg/24 hr*			
		0 to 79	80 to 149	150 to 499	≥500
Satisfactory	214 (100%)	32%	28%	30%	10%
Fair	150 (100%)	30%	22%	35%	13%
Poor	146 (100%)	20%	21%	33%	26%

[a] Percentages are given for each appraisal of control; see **Methods** for definition of diabetic control.

Marked hyperglycemia can cause proteinuria which reverts to normal after adequate diabetic control [7, 8, 31]. This was true in some patients but even with satisfactory control, 40% of this study's patients still had excessive protein excretion.

Although subjects with a tendency to heart failure were treated, it cannot be excluded that minimal cardiac decompensation may have contributed to the proteinuria in some of them. Hypertension can also cause proteinuria [32], but it is reasonable to assume that diabetes mellitus rather than hypertension was responsible for excessive excretion of urinary proteins. Indeed, only 42% of the diabetic patients with strictly normal BP had a 24-hr protein excretion rate within the normal range.

Clinical evolution and comparison with juvenile onset diabetes mellitus. The histopathological picture of diabetic nephropathy is essentially the same in maturity onset, noninsulin-dependent diabetes mellitus (type 2) and in juvenile onset, insulin-dependent diabetes mellitus (type 1). The clinical course of the renal involvement, however, is generally different according to the age of onset of the disease.

Among this study's patients examined less than one year after the diagnosis, 37% had abnormal protein excretion and a further 24% had increased excretion of albumin or HMW proteins. In contrast, most juvenile onset diabetic patients maintain a strictly normal excretion pattern of urinary proteins over a longer period [6, 7]. The proportion of excessive protein excretion in young patients, as reported by White, was under 2% during the first 10 years after the beginning of diabetes mellitus [33]. In the same study, this proportion reached 40% between 20 and 29 years after the onset of diabetes mellitus creating a twenty-fold increase. Among this study's maturity-onset patients, the increase was hardly two-fold after 20 years or more of evolution.

The proteinuria of the older diabetic patients remained usually moderate, exceeding 3 g/24 hr in only 3.5% of the patients. The proportion of nephrotic syndrome was no more than 1.8%, compared to 45% in juvenile onset diabetic patients 20 to 50 years old at death [1].

In juvenile onset diabetes mellitus, the proteinuria appeared late and usually heralded major kidney involvement; death from renal failure occurred in nearly 40% of the patients during the 10 years following the onset of permanent proteinuria [2, 33, 34]. With maturity onset diabetes mellitus, however, most of the patients in our study maintained adequate GFR, even though

proteinuria had been recorded for many years, and there was only one death from renal insufficiency. This is all the more striking in view of the high percentage of long standing (Table 1) and poorly controlled (Table 5) diabetes mellitus.

Many patients with long-standing diabetes mellitus showed normal protein excretion and also frequently a normal GFR. This was the case in 38 out of 90 patients affected by diabetes mellitus for over 16 years. Yet, these were not necessarily cases of easily controlled diabetes mellitus: Twenty-one patients received insulin, and in 13 cases blood glucose sometimes exceeded 300 mg/dl (16.7 mmoles/liter), while only 10 patients had fasting blood glucose persistently below 200 mg/dl (11 mmoles/liter). However, only 11 of these 38 patients with long-standing diabetes mellitus without proteinuria had hypertension (that is, 29% as compared to 52% of the patients with diabetes mellitus of the same duration but with proteinuria).

In 166 diabetes mellitus patients of this series, the set of renal tests was repeated two to six times over periods of 2 to 9 years [35]. In most of the patients, the protein excretion and the GFR remained quite stable. A fall of the GFR exceeding 10 ml/min per year was noted in only 13%.

The kidney in maturity onset diabetes mellitus thus responds differently than in juvenile onset diabetes mellitus. The response is characterized by frequent early proteinuria and slow progression, as opposed to the late occurring proteinuria followed by relatively rapid evolution toward uremia that is so prominent a feature of juvenile onset diabetes mellitus. Thus, the question of whether or not the very lack of insulin might be an important factor in the pathogenesis of diabetic nephropathy is raised. Mechanisms such as increased glycosylation could be involved [36]. In addition, the more benign course in older patients may be related to some, as yet uncertain, protective mechanisms, and may be linked to HLA-genetic factors [37], even though more (rather than less) risk factors related to circulatory disorders and senescence are to be anticipated.

Hypertension. Overestimation of BP was limited by using a long cuff with a broad bladder in obese patients. Only cases of clearly established hypertension, with several diastolic readings of 110 mm Hg or more before anti-hypertensive treatment, were considered for comparison with normotensive patients. In all age groups, hypertension was found approximately twice as often in diabetic patients as in other patients of our outpatient clinic [38], in accordance with most [1, 39, 40] but not all [41] other series of diabetic vs. nondiabetic patients. These discrepancies are most likely due to differences in the selection of groups as well as the influence of antihypertensive treatment, which is not always specified.

Why such a high prevalence of hypertension should occur in diabetes mellitus is poorly understood; this study suggests the coexistence of several factors. Hypertension was generally considered to be essential and coincidental when diagnosed before or simultaneously with the onset of diabetes mellitus. This eventuality represents 28% of the entire study group, a proportion comparable to the general population of that age [42]. Furthermore, obesity, a prominent finding in maturity onset diabetes mellitus, is in relation to hypertension [43]. In the case of diabetic patients, however, who were normotensive at the time of diagnosis, it is possible that diabetes mellitus played a role in the subsequent development of hypertension. A likely mechanism is the occurrence of diabetic nephropathy, which may be the cause of hypertension even in young diabetic patients. Two of the patients had clinical, radiological, and biological findings compatible with renovascular hypertension. But other publications show evidence that this etiology of hypertension in diabetic patients accounts for a small proportion of patients even though some degree of stenosis of renal arteries is noted quite frequently [44].

Signs of renal involvement are seen more often when hypertension is associated with diabetes mellitus. For example, 14% of hypertensive diabetes mellitus patients had a GFR below 60 ml/min while this was the case in only 4% of normotensive diabetics. It is, of course, quite difficult to establish whether or not hypertension was the cause or the consequence of altered renal function. Yet, the proportion of cases with GFR below 60 ml/min was three times higher in hypertensive patients who subsequently developed diabetes mellitus than in normotensive diabetics. Furthermore, patients with a long duration of diabetes mellitus who retained normal renal function are predominantly normotensive. Therefore, it is likely that arterial hypertension is an aggravating factor in the prognosis of renal involvement in diabetes mellitus [45].

Urinary infection, as evidenced by the presence of 10^5 or more micro-organisms per milliliter of urine was found in 19% of diabetes mellitus patients (mostly women) on the day that renal function tests were performed. About one third of the remainder had a history of urinary infection. It is well known that diabetic patients with urinary infection are more prone to develop pyelonephritis as well as papillary necrosis, a frequent and dreaded occurrence in diabetes mellitus. There is a correlation between urinary infection and the tubular electrophoretic pattern of the urinary proteins, as well as with the excessive excretion of lysozyme. These findings are often accompanied by clinical and radiological signs of pyelonephritis, and consequently, they provide a high index of suspicion of such an event. The opposite does not apply, however, because the majority of our patients with pyelonephritis or papillary necrosis had proteinuria of the glomerular or mixed type, presumably caused by concomitant glomerulosclerosis.

Effect of diabetic control. The interpretation of the inverse correlation between renal involvement and quality of diabetic control is difficult. Could this be the welcome result of a good treatment? Or may it simply be attributed to the fact that some forms of diabetes mellitus are less aggressive and lead, simultaneously but independently, to easier control of blood glucose and less involvement of target organs? This study's findings do not clearly answer these questions, all the more so as there is a slight but significant correlation between blood glucose levels and the duration of diabetes mellitus ($P < 0.01$). However, it has been shown by convincing studies that good control of diabetes mellitus improves the prognosis [46].

Conclusion. The study of a large group of patients showed that the prognosis of diabetic nephropathy in maturity onset, noninsulin-dependent diabetes mellitus is relatively good, unlike that of the juvenile onset, insulin-dependent diabetes mellitus. Available data suggested that it is worthwhile to correct not only blood glucose but also hypertension [45] and urinary infection [47] in the effort to improve the course of diabetic nephropathy. It should be remembered, however, that the ultimate prognosis in old patients depends on the cardiovascular system and not on the kidneys [1, 2, 21].

Summary. The purpose of this study was to quantify the clinical manifestations of renal involvement in maturity onset diabetes mellitus. Of 510 patients with the diagnosis of diabetes mellitus made after the age of 40, 48% had increased abnormally protein excretion. Even when it remained in normal range, the rate of protein excretion in the urine tended to exceed that found in control persons; sodium dodecylsulfate-polyacrylamide gel electrophoresis frequently revealed increased excretion of albumin and high and low molecular weight proteins. Lysozymuria or tubular electrophoretic patterns of the urinary proteins provided a suspicious index of pyelonephritis. Control persons excreted more protein in the upright position than in recumbency, a finding that was less evident in diabetic patients. Arterial diastolic hypertension at 110 mm Hg or above before treatment was noted in 46% of the diabetic patients and correlated with more severe renal involvement. An association of proteinuria with poor glycemic control and with the duration of diabetes mellitus was also noted. Although diagnosed less than one year earlier, 37% of the patients already had an excess of protein excretion; in most the GFR remained normal for many years and was less than 60 ml/min/1.73 m^2 in only 43 cases. A group of elderly patients had absolutely normal renal function in spite of diabetes mellitus of more than 16 years' duration. Thus, the prognosis of renal involvement in maturity onset noninsulin-dependent diabetes mellitus is relatively better than that in juvenile onset insulin-dependent diabetes mellitus. Control not only of blood glucose but also of hypertension and urinary infection appears mandatory for slowing down the course of diabetic nephropathy.

Acknowledgments

We thank Prof. A. Renold, Dr. E. Trimble and Dr. J.-Ph. Assal for a critical review of this manuscript; Mrs. J. Spahr, R. Striberni, and M. Tillolès for technical assistance; the students who helped in preparation of the data; Mrs. I. Weber and D. Rey for secretarial assistance; Prof. F. Chatelanat for histological examinations; Prof. A. Donath for isotopical tests; and the residents of the Policlinic of Medicine who observed the patients.

Reprint requests to Prof. J. Fabre, Policlinique de médecine, Hôpital Cantonal Universitaire, CH-1211 Geneva 4, Switzerland

References

1. Bell ET: Renal vascular disease in diabetes mellitus. *Diabetes* 2:376–389, 1953
2. Balodimos MC: Diabetic nephropathy, in *Joslin's Diabetes Mellitus* (11th ed), edited by Marble A, White P, Bradley RF, Krall LP, Philadelphia, Lea & Febiger, 1971, pp. 526–561
3. Arieff AI: Kidney, water and electrolyte metabolism in diabetes mellitus, in *The Kidney,* edited by Brenner BM, Rector FC, Philadelphia, W. C. Saunders, 1976, pp. 1259–1296
4. Mauer SM, Steffes MW, Brown DM: The kidney in diabetes. *Amer J Med* 70:603–612, 1981
5. Assal JP, Froesch ER: Das Pankreas, in *Klinik der inneren Sekretion* (3rd ed), edited by Labarth A, Berlin, Heidelberg, New York, Springer, 1978, pp. 689–804
6. Mogensen CE, Andersen MJF: Increased kidney size and glomerular filtration rate in untreated juvenile diabetes: Normalization by insulin-treatment. *Diabetologia* 11:221–224, 1975
7. Mogensen CE: Renal function changes in diabetes. *Diabetes* 25:872–879, 1976
8. Viberti GC: Early functional and morphological changes in diabetic nephropathy. *Clin Nephrol* 12:47–53, 1979
9. Savory J, Pu PH, Sunderman FW: A biuret method for determination of protein in normal urine. *Clin Chem* 14:1160–1171, 1968
10. Poortmans JR, Jeanloz RW: Quantitative immunological determination of 12 plasma proteins excreted in human urine collected before and after exercise. *J Clin Invest* 47:386–393, 1968
11. Manuel Y, Revillard JP: Study of urinary proteins by zone electrophoresis. Methods, in *Proteins in Normal and Pathological Urine,* edited by Manuel Y, Revillard JP, Bétuel H, Basle, Karger, 1970, p. 153–159
12. Scheidegger JJ: Une micro-méthode de l'immunoélectrophorèse. *Int Arch Allergy* 7:103–109, 1955
13. Ballant L, Mulli JC, Fabre J: Urinary protein analysis with sodium dodecylsulfate polyacrylamide gel electrophoresis—a comparison with other analytical techniques. *Clin Chim Acta* 54:27–37, 1974
14. Cao A, Balant L, Fabre J, Canavese JC: La protéinurie physiologique. Données de l'électrophorèse sur gel d'acrylamide-SDS et d'autres méthodes d'analyse qualitative et quantitative. *Schweiz Med Wochenschr* 105:421–429, 1975
15. Manuel Y, Revillard JP: Study of urinary proteins by zone electrophoresis. Principles of interpretation, in *Proteins in Normal and Pathological Urine,* edited by Manuel Y, Revillard JP, Bétuel H, Basle, Karger, 1970, p. 159–171
16. Mulli JC, Balant L, Giromini M, Fabre J: Analysis of proteinuria in health and disease using sodium dodecylsulfate polyacrylamide gel electrophoresis. *Europ J Clin Invest* 4:253–259, 1974
17. Wauters JP, Favre H: L'intérêt de la mesure du lysozyme urinaire dans le diagnostic des néphropathies. *Schweiz Med Wochenschr* 100:1903–1907, 1970
18. Favre H: Determination des fonctions rénales par la technique de l'injection unique. *J Urol Nephrol* 79:1007–1052, 1973
19. Hamburger J, Mathé G, de Vergizier M: Note sur une méthode de numération des éléments figurés des urines. *Ann Biol Clin* 8:627–631, 1950
20. Bishop YM, Fienberg SE, Holland PW: *Discrete Multivariate Analysis. Theory and Practice.* Cambridge, Massachusetts, and London, The MIT Press, 1978
21. Vernet A, Fabre J, Mulli JC: Facteurs de risque artériel et rénal dans le diabète. *Schweiz Med Wochenschr* 105:296–303, 1975
22. Mogensen CE: Urinary albumin excretion in early and long-term juvenile diabetes. *Scand J Clin Lab Invest* 28:183–193, 1971
23. Panzram G, Anger G, Wöllner H: Untersuchungen über die physiologische Proteinurie beim Diabetes mellitus. *Dtsch Med Wochenschr* 92:1013–1016, 1967
24. Keen H, Chlouverakis C: Urinary albumin excretion and diabetes mellitus. *Lancet* 2:1155–1156, 1964
25. De Seigneux R, Schwarz R, Balant L, Fabre J: Aspects initiaux des altérations de la protéinurie chez les diabétiques. *Schweiz Med Wochenschr* 110:295–301, 1980
26. Boesken WH, Kopf K, Schollmeyer P: Differentiation of proteinuric diseases by discelectrophoretic molecular weight analysis of urinary proteins. *Clin Nephrol* 1:311–318, 1973
27. Lopez Virella MF, Virella G, Rosebrock G, Sagel J, Gonzalez J, Colwel J: Early diagnosis of renal malfunction in diabetics. Abnormal proteinuria revealed by sodium dodecylsulfate polyacrylamide gel electrophoresis. *Diabetologia* 16:165–171, 1979
28. Ducrey J, Fabre J, Balant L, Leblanc A, Duvivier E: La protéinurie dans le diabète de la maturité. Analyse quantitative et qualitative. *Schweiz Med Wochenschr* 105:1138–1144, 1975
29. Pelz KS, Gottfried SP, Pay E: Kidney function in old men and women. *Geriatrics* 20:145–149, 1965
30. Gellmann DD, Pirani CL, Soothill JF, Muehrcke RC, Kark RM: Diabetic nephropathy: A clinical and pathologic study based on renal biopsies. *Medicine* 38:321–367, 1959
31. Viberti GC, Pickup JC, Jarrett RJ, Keen H: Effect of control of blood glucose on urinary excretion of albumin and β_2 microglobulin in insulin-dependent diabetes. *New Engl J Med* 300:638–641, 1979
32. Yamada T, Ishihara M, Ichikawa K, Hiramatsu K: Proteinuria and renal function during antihypertensive treatment for essential hypertension. *J Am Geriat Soc* 28:114–117, 1980
33. White P: Natural course and prognosis of juvenile diabetes. *Diabetes* 5:445–450, 1956
34. Caird FI: Survival of diabetics with proteinuria. *Diabetes* 10:178–181, 1961

35. RICK JR: L'évolution des fonctions rénales dans le diabète de la maturité. *Thèse de Genève*, 1982
36. SPIRO RG: Search for a biochemical basis of diabetic microangiopathy. Claude Bernard lecture. *Diabetologica* 12:1–14, 1976
37. CUDWORTH AG: Type 1 diabetes mellitus. *Diabetologia* 14:281–286, 1978
38. VERNET A, FABRE J, MÉRIER G: Diabète sucré et hypertension artérielle. *Rev Suisse Méd* 64:583–588, 1975
39. PELL S, D'ALONZO CA: Factors associated with long-term survival of diabetes. *JAMA* 214:1833–1840, 1970
40. BLOOM A: Relation of the complications of diabetes to the clinical state. *Proc Roy Soc Med* 60:149–152, 1967
41. KEEN H, TRACK NS, SOWRY GSC: Arterial pressure in clinical apparent diabetes. *Diabète et Métabolisme* 1:159–178, 1975
42. BÜHLER FR, DE LÈCHE AS, SCHÜLER G, GUTZWILLER F, BAUMANN F, SCHWEIZER W: Das Hypertonieproblem in der Schweiz. Analyse einer Blutdruckuntersuchung an 21 589 Personen. *Schweiz Med Wochenschr* 106:99–107, 1976
43. KANNEL WB, BRAND N, SKINNER JJ, DAWBER TR, MCNAMARA PM: The relation of adiposity to blood pressure and the development of hypertension. *Ann Intn Med* 67:48–58, 1967
44. MUNICHOODAPPA D, D'ELIA JA, LIBERTINO JA, GLEASON RE, CHRISTLIEB AR: Renal artery stenosis in hypertensive diabetics. *J Urol* 121:555–558, 1978
45. MOGENSEN CE: Progression of nephropathy in long-term diabetics with proteinuria and effect of initial anti-hypertensive treatment. *Scand J Clin Lab Invest* 36:383–388, 1976
46. TCHOBROUTSKY G: Prevention and treatment of diabetic nephropathy, in *Advances in Nephrology*, edited by HAMBURGER J, CROSNIER J, GRÜNFELD JP, MAXWELL MH, Chicago, Year Book Medical Publishers, 1979, vol. 9, pp. 63–86
47. VEJLSGAARD R: Studies on urinary infection in diabetics. II. Significant bacteriuria in relation to long-term diabetic manifestations. *Acta Med Scand* 179:183–188, 1966