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Patterns of renal injury in NIDDM patients with microalbuminuria

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Summary Microalbuminuria predicts overt nephropathy in non-insulin-dependent diabetic (NIDDM) patients; however, the structural basis for this functional abnormality is unknown. In this study we evaluated renal structure and function in a cohort of 34 unselected microalbuminuric NIDDM patients (26 male/8 female, age: 58 ± 7 years, known diabetes duration: 11 ± 6 years, HbA_{1c}: 8.5 ± 1.6 %). Systemic hypertension was present in all but 3. Glomerular filtration rate (GFR) was 101 ± 27 ml · min^{-1} · 1.73 m^{-2} and albumin excretion rate (AER) 44 (20–199) μg/min. Light microscopic slides were categorized as: C I) normal or near normal renal structure; C II) changes "typical" of diabetic nephropathology in insulin-dependent diabetes (IDDM) (glomerular, tubulo-interstitial and arteriolar changes occurring in parallel); C III) "atypical" patterns of injury, with absent or only mild diabetic glomerular changes associated with disproportionately severe renal structural changes including: important tubulo-interstitial with or without arteriolar hyalinosis with or without global glomerular sclerosis. Ten patients (29.4 %) were classified as C I, 10 as C II (29.4 %) and 14 as C III (41.2 %); none of these patients had any definable non-diabetic renal disease. GFR, AER and blood pressure were similar in the three groups, while HbA_{1c} was higher in C II and C III than in C I patients. Diabetic retinopathy was present in all C II patients (background in 50 % and proliferative in 50 %). None of the patients in C I and C III had proliferative retinopathy, while background retinopathy was observed in 50 % of C I and 57 % of C III patients. In summary, microalbuminuric NIDDM patients are structurally heterogeneous with less than one third having "typical" diabetic nephropathology. The presence of both "typical" and "atypical" patterns of renal pathology was associated with worse metabolic control, suggesting that hyperglycaemia may cause different patterns of renal injury in older NIDDM compared to younger IDDM patients. [Diabetologia (1996) 39: 1569–1576]

Keywords NIDDM, renal structure, microalbuminuria, glomerular filtration rate.

Diabetic nephropathy is the single most frequent cause of end-stage renal disease in western countries, and the proportion of uraemic patients who are diabetic has been increasing in recent years [1, 2]. The United States Renal Data System does not yet separate insulin-dependent (IDDM) from non-insulin-dependent (NIDDM) diabetes mellitus. The European Dialysis and Transplant Association Registry reported that 35 % of diabetic patients requiring renal replacement therapy have NIDDM [2]; however, lack of precision in diabetes classification, originating from insulin-treated (non-insulin-dependent) patients, often classified as having IDDM, may have caused an underestimation of the percent of uraemic diabetic patients affected by NIDDM [3]. Indeed, regional surveys have shown a higher proportion of NIDDM patients on renal replacement therapy, both in the United States [4] and in Europe [3, 5, 6]. In Italy, when diabetes was classified by a specific

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Abbreviations: IDDM, Insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; DN, diabetic nephropathy; GFR, glomerular filtration rate; AER, albumin excretion rate; PAS, periodic acid-Schiff.

questionnaire, the proportion of uraemic NIDDM patients rose to 67 % [6]. Although a large proportion of diabetic patients receiving renal replacement therapy have NIDDM, the pathology and natural history of diabetic nephropathy (DN) in NIDDM is still unclear. The clinical manifestations of DN, proteinuria, declining glomerular filtration rate (GFR) and increasing blood pressure, are similar in IDDM and NIDDM [7, 8]; nevertheless, whether these clinical features are consequences of similar underlying renal lesions is unknown. In IDDM, glomerular, arteriolar, tubular and interstitial structural lesions occur largely in parallel, although glomerulopathy is functionally the most important change [9–14]. Quantitative morphometric studies have demonstrated that the lesion most closely related to the decline in renal function in IDDM is mesangial expansion, especially mesangial matrix accumulation [13, 15]. Also, we have recently reported, in a longitudinal study with sequential renal biopsies performed 5 years apart in IDDM patients, that the only morphometric parameter associated with increasing albuminuria was mesangial fractional volume [14]. The structural changes occurring in the arterioles, tubules and interstitium are usual concomitants, typically in proportion to the degree of glomerulopathy, and become severe only when glomerulopathy is advanced; in fact advanced global glomerular sclerosis, interstitial fibrosis and arteriolopathy in the absence of abvanced glomerulopathy are uncommon in IDDM.

Non-diabetic renal disease is uncommon in patients who have had IDDM for 10 or more years with overt nephropathy (personal observations), while the prevalence of non-diabetic renal lesions has been reported to be high in proteinuric NIDDM patients (approximately 30 %). Parving et al. [16] reported that 8 of 35 (23 %) NIDDM patients with proteinuria had non-diabetic glomerulopathies which these authors classified as minimal lesion nephropathy, mesangio-proliferative glomerulonephritis and its sequelae. Heterogeneity in renal lesions has also been reported by Gambara et al. [17] who found that only 19 of 52 (37 %) of proteinuric NIDDM patients had typical changes of DN. An autopsy study did not confirm these finding [18].

Microalbuminuria antedates clinical proteinuria in both IDDM [19–21] and NIDDM [22, 23]; however, only approximately 20 % of NIDDM patients with microalbuminuria progress to overt nephropathy over a decade of follow-up in contrast to over 80 % of IDDM patients [23]. Indeed microalbuminuria in NIDDM is a better predictor of cardiovascular mortality than uraemia [22, 24, 25]. The low predictive value of microalbuminuria for overt proteinuria in NIDDM may in part be explained by the high mortality for cardiovascular disease, which prevents the progression to clinical nephropathy. However, it has also been hypothesized that microalbuminuria in NIDDM patients may be either consequent to diabetic glomerulopathy, as in IDDM, or reflect generalized endothelial dysfunction [8, 26]. This latter hypothesis remains speculative, since to date no information is available on renal structure in NIDDM patients with microalbuminuria.

The present study investigates renal function and structure in 34 microalbuminuric NIDDM patients in order to describe the renal structural concomitants of this functional disturbance.

Subjects and methods

Patients. The patients were participating in an ongoing multicenter study of renal structural-functional relationships in NIDDM. Patients were referred to the University of Padova from diabetes centres in the north-east of Italy for research evaluation of renal structure and function, based upon the following criteria.

1. Age 70 years or less.
2. Age at diagnosis of NIDDM 40 years or more. Diabetic patients were diagnosed as having NIDDM when onset was after age 40 years, when they were treated with diet alone or in association with oral hypoglycaemic agents and/or insulin and when they were not receiving insulin in the first 2 years after diagnosis. Insulin-treated patients with normal body weight had a glucagon test performed to confirm the diagnosis of NIDDM (when C-peptide levels were normal).
3. Known duration of NIDDM 2 years or more.
4. Serum creatinine < 180 μmol/l.
5. Absence of other obvious renal diseases including serious stone disease, and presence of single kidney.
6. Secondary causes of hypertension including known renal artery stenosis and endocrinopathy.
7. Requirement for systemic anticoagulation (heparin or coumadin).

Otherwise all patients willing to participate were accepted regardless of renal function. In no case were renal biopsies performed for clinically indicated diagnostic purposes.

To date light microscopic slides from 34 microalbuminuric patients have been evaluated and are presented here. Patients were defined as microalbuminuric when AER was 20 μg or more/min but 200 μg or less/min in at least two of three consecutive sterile 24-h urine collections.

These studies were approved by the ethical committee of the University of Padova. Patients gave written informed consent before each study. The patients were admitted to the Department of Internal Medicine at the University of Padova Hospital where percutaneous renal biopsy and renal functional studies were performed. In patients on antihypertensive treatment, the therapy was withdrawn 3–5 days before and during admission; after the studies were completed, patients were returned to their previous therapy. During admission patients underwent at least three 24-h urine collections for measurements of AER after urine cultures were determined to be sterile. If bacterial growth was present, treatment was initiated and urine collections were repeated for determination of AER on sterile urine samples. Microscopic examination of the urinary sediment was performed. Glomerular filtration rate was determined by the plasma clearance of Cr-EDTA, as described in detail elsewhere [27]. Blood pressure was measured at least 10 times with the patient in the supine position. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Patients

were defined hypertensive when the blood pressure values exceeded 140/85 mm Hg [28], or when on antihypertensive therapy regardless of BP levels. HbA_{1c} was measured to assess metabolic control. All patients had funduscopy performed through dilated pupils in the Department of Ophthalmology of the University of Padova and, when required, fluoroangiographic studies. Patients were classified as follows: 1) absence of diabetic retinopathy; 2) background diabetic retinopathy; 3) proliferative diabetic retinopathy.

Normal control subjects. Kidney biopsies were obtained from 36 (17 male /19 female) kidney donors at the time of renal transplantation at the University of Minnesota. Thirty-three of these donors were living related donors and three were cadavers; these control subjects were matched for age with the diabetic patients (age: 55.7 ± 7 years, range: 45.1–69).

Analytical procedures. HbA_{1c} values were measured by high-performance liquid chromatography (DIAMAT Analyzer, BIO-RAD, Calif., USA). AER was measured by radioimmunoassay. ^{51}Cr radioactivity was measured in duplicate 1-ml aliquots of plasma in a gamma counter (Cobra-5002 CPM, Camberra Packard, Milan, Italy) with the energy window set to 240–400 KeV [27].

Renal structure. Kidney biopsies were performed under ultrasound guidance by experienced investigators. Safety requirements included normal blood pressure levels (≤ 140/85 mm Hg) at the time of the biopsy as well as normal coagulation studies and platelet counts. Aspirin or other antiplatelet agents were withdrawn 2 weeks before the biopsy. After kidney biopsy, tissue was immediately examined under a dissecting microscope to ensure adequate numbers of glomeruli.

Light microscopy. Most of the core was placed in Zenker's fixative, embedded in paraffin and processed for light microscopy [29]. Light microscopy sections (2-μm thick) were stained with haematoxylin and eosin and periodic acid Schiff (PAS). PAS sections from all patients and normal control subjects were concomitantly and blindly evaluated by two observers, in order to develop a qualitative overview of the patterns of injury. The two observers evaluated the light microscopy slides simultaneously, and therefore an agreement on the categorization was discussed and made at the time of the reading. Based on the resultant overview of the biopsy material the following classification was developed:

Category C I): Normal or near normal renal structure. These patients had biopsies which were normal or showed very mild mesangial expansion, tubulo-interstitial changes or arteriolar hyalinosis in any combination (Fig. 1A).

Category C II): Typical diabetic nephropathology. These patients had established diabetic lesions with balanced severity of glomerular, tubulo-interstitial and arteriolar changes. This picture is typical of that seen in IDDM patients with obvious light microscopic DN changes (Fig. 1B).

The severity of lesions in the different compartments, as well as the possible heterogeneity among different glomerular profiles, was evaluated as described elsewhere [13]. Quantitative morphometric measures of mesangial ($r = 0.87$, $p < 0.0001$) [13] and interstitial expansion ($r = 0.90$, $p < 0.0001$) [30] are closely correlated with the semiquantitative light microscopic analysis. Our previous studies have shown highly significant correlations between glomerular lesions, interstitial expansion, arteriolar hyalinosis and global glomerular sclerosis [11, 13, 31].

Category C III): Atypical patterns of renal injury. These patients had absent or only mild glomerular diabetic changes with disproportionately severe renal structural lesions including:

(a) Tubular atrophy, tubular basement membrane thickening and reduplication and interstitial fibrosis (tubulo-interstitial lesions) (Fig. 1C).

(b) Advanced glomerular arteriolar hyalinosis commonly associated with atherosclerosis of larger vessels (Fig. 1D).

(c) Global glomerular sclerosis (> 25 %) in the presence of absent or mild mesangial expansion (index of mesangial expansion ≤ 0.5 according to our score system [13]) (Fig. 1E).

These patterns were present in any possible combination. Considering the complexity of the patterns of injury and the limited number of patients, we pooled these three groups (a, b, c) into one single category (C III).

It should be noted that patients in categories III and II could have similar levels of diabetic glomerulopathy, expressed as index of mesangial expansion, but those in C III had disproportionately severe tubulointerstitial, vascular or glomerulosclerotic lesions.

Immunofluorescent microscopy. One 2–3 mm cortical core was snap frozen for immunofluorescence studies. The tissue was blindly examined using rabbit or goat antisera specifically reactive to human IgA, IgG, IgM, fibrinogen, C3, C4, C1q.

Electron microscopy. Three 1-mm cortical cores were placed in 2.5 % glutaraldehyde in Millonig's buffer and processed for electron microscopy [29]. Ultrathin sections were obtained on an LKB ultramicrotome (LKB, Bromma, Sweden) and observed on a Hitachi H/600 elecron microscope (Hitachi, Tokyo, Japan). Three glomeruli per biopsy were examined and pictures taken at final magnifications of 3900 × and 12 000 ×, as previously described [32]. Electron microscopic morphometric analysis is in progress. Photomicrographs obtained at 12 000 × were analysed for diagnostic purposes.

None of the patients in the three groups described above had light immunofluorescent or electron microscopy findings of any definable renal disease other than typical diabetic nephropathy or the patterns described above.

Statistical analysis

Data are expressed as mean ± 1SD. Values for AER, not normally distributed, were logarithmically transformed before analysis and are expressed as median and range. Comparisons among the diabetic groups first used a one-way analysis of variance (ANOVA) and then unpaired Student's *t*-test for parameters shown to be different by ANOVA. Values of $p < 0.05$ were considered significant.

Results

Clinical features of patients. Twenty-six of the 34 patients (all Caucasian) were males. Age was 58.5 ± 7.3 years (mean ± 1SD) and known NIDDM duration was 10.8 ± 6.3 years. Body mass index (BMI) was 28.9 ± 3.9 kg/m^2 (normal values in a group of age-matched normal control subjects: 24 ± 2) and HbA_{1c} was 8.5 ± 1.6 % (normal range: 4.1–6.1 %). GFR was 101 ± 27 ml · min^{-1} · 1.73 m^{-2} (normal range in a

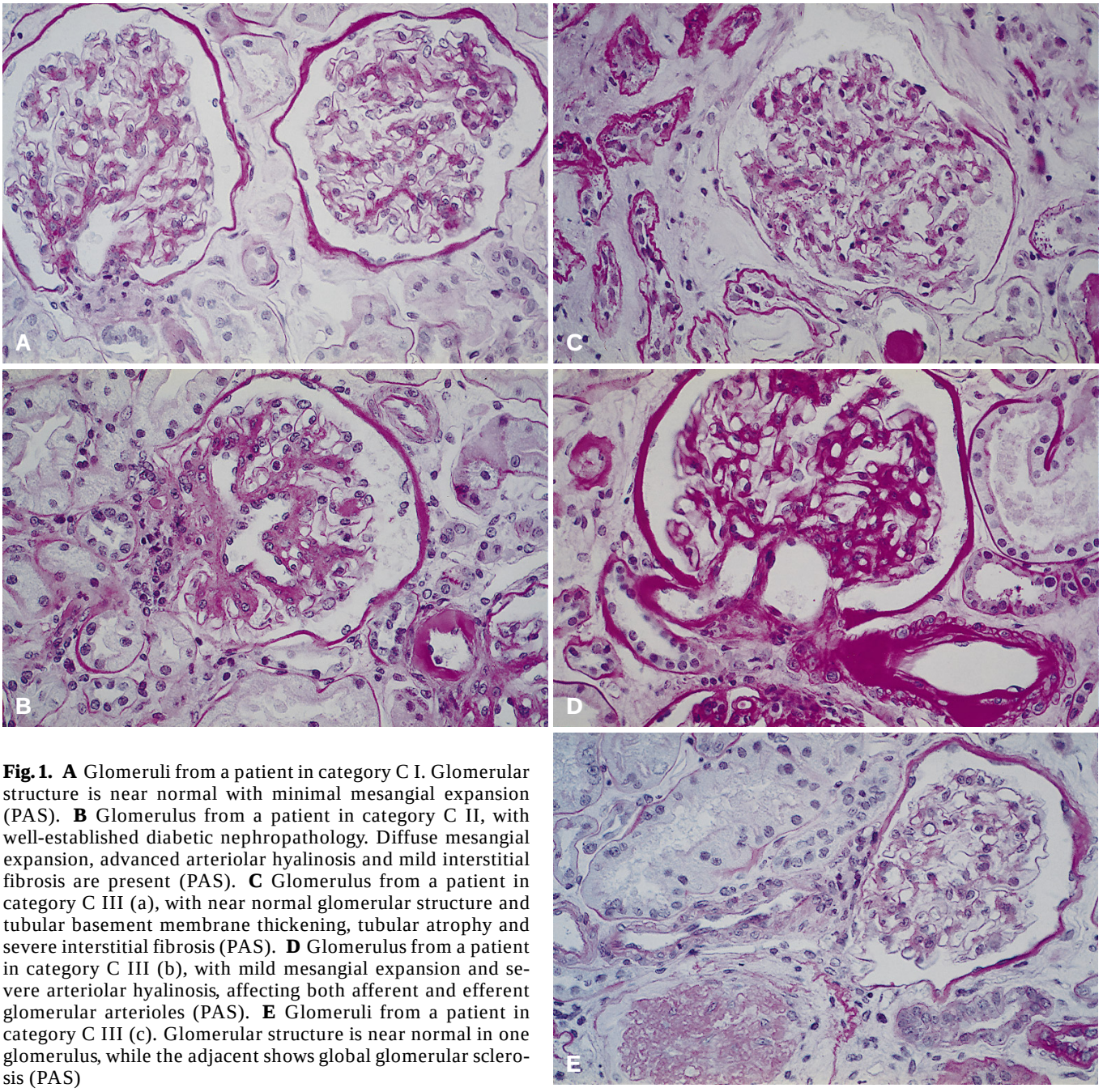

Fig. 1. **A** Glomeruli from a patient in category C I. Glomerular structure is near normal with minimal mesangial expansion (PAS). **B** Glomerulus from a patient in category C II, with well-established diabetic nephropathology. Diffuse mesangial expansion, advanced arteriolar hyalinosis and mild interstitial fibrosis are present (PAS). **C** Glomerulus from a patient in category C III (a), with near normal glomerular structure and tubular basement membrane thickening, tubular atrophy and severe interstitial fibrosis (PAS). **D** Glomerulus from a patient in category C III (b), with mild mesangial expansion and severe arteriolar hyalinosis, affecting both afferent and efferent glomerular arterioles (PAS). **E** Glomeruli from a patient in category C III (c). Glomerular structure is near normal in one glomerulus, while the adjacent shows global glomerular sclerosis (PAS)

group of 19 age and sex-matched normal control subjects: 85–135) and AER was 44 (20–199) μg/min (median, range) (normal values: 5 [0–14]).

All but 6 patients were receiving antihypertensive therapy, and the majority of them were on ACE inhibition. Overall, only 3 patients were normotensive, according to the criteria described above.

Based on the light microscopic findings 10 patients (5 male/5 female) were allocated to category I (29.4 %), 10 patients (9 male/1 female) to category II (29.4 %) and 14 (10 male/2 female) to category III (41.2 %). Important tubulo-interstitial changes were observed in all but 1 patient, who had very severe arteriolar hyalinosis lesions, in category III; these tubulo-interstitial lesions were often associated with arteriolar changes and in some (n = 3) patients to severe (> 25 %) global glomerular sclerosis.

The frequency of global glomerular sclerosis was 0 (0–20) (median, range) in CI, 0 (0–36) in CII and 4 (0–46) in CIII.

The clinical features of the patients as divided into the three structural groups are summarized in Tables 1 and 2.

CI patients tended to be younger than patients in groups CII and CIII, although the difference was not significant by ANOVA (p = 0.13); 50 % of patients in

Table 1. Clinical features of patients divided into three renal structural categories

Category	male/female	%	Age (years)	Known NIDDM duration (years)	BMI (kg/m^2)	HbA_{1c} (%)
C I	5/5	23.4	54 ± 9	8 ± 3	31 ± 4[b]	7.5 ± 0.8
C II	9/1	29.4	60 ± 6	14 ± 6[a]	26 ± 4	9.6 ± 1.8[d]
C III	12/2	41.2	61 ± 6	10 ± 8	30 ± 3[b]	8.5 ± 1.3[c]
p values						

Data are mean ± SD
[a] $p < 0.05$ vs C I and C III; [b] $p < 0.03$ vs C II; [c] $p < 0.05$ vs C I; [d] $p < 0.005$ vs C I

Table 2. Renal function and blood pressure of patients divided into three renal structural categories

Category	AER (μg/min)	GFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	Blood pressure	
			Systolic (mmHg)	Diastolic (mmHg)
C I	45 (20–198)	111 ± 20	142 ± 19	91 ± 10
C II	50 (22–190)	91 ± 36	154 ± 13	92 ± 7
C III	39 (20–198)	101 ± 21	155 ± 16	90 ± 10

Data are mean ± SD (AER is median and range) NS for all comparisons

Table 3. Diabetic retinopathy in relation to patterns of renal injury

Category	Diabetic retinopathy		
	Absent	Background	Proliferative
C I	5	5	0
C II	0	5	5
C III	6	8	0

CI were females, while in groups CII and CIII there was a clear preponderance of males (Table 1). Known duration of NIDDM tended to be different among groups (ANOVA, $p = 0.08$), with group CII patients having the longest duration (*t*-tests, $p < 0.05$ vs CI and CIII). HbA_{1c} levels were significantly different among groups (ANOVA, $p < 0.01$); subsequent analysis showed that CII and CIII patients had higher HbA_{1c} values than CI patients (*t*-tests, $p < 0.005$ and $p < 0.05$, respectively). BMI was also different among groups (ANOVA, $p < 0.02$); BMI was only mildly increased in CII patients (range: 18.1–31.5) and was significantly higher in CI (range: 27.7–40.1) and CIII patients (24.5–35.1) compared to CII (*t*-tests, $p < 0.05$ for both). AER levels were superimposable in the three groups (Table 2). GFR was not different in the three groups of patients; however, 5 of the 10 patients in CII had GFR values under $85\ ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ compared to 1 of 10 in CI and 2 of 14 in CIII. Systolic and diastolic blood pressure values were similar in the three groups; two of the 3 normotensive patients were in group CI and one in group CIII. Seven of 10 patients in group CI, 10 of 10 in group CII and 11 of 14 in group CIII were receiving antihypertensive therapy.

Results of the funduscopic or fluoroangiographic evaluations are given in Table 3. In several patients varying degrees of hypertensive retinopathy were present with or without diabetic retinopathy.

Normal control subjects. Based on the scores for interstitial fibrosis, 3 of 36 (8 %) subjects had important tubulo-interstitial changes. Several normal control subjects had mild arteriolar hyalinosis lesions; 6 (16 %) had more advanced arteriolar lesion scores, comparable to those observed in patients in categories II and III (scores ≥ 1.0 according to our previously described scoring system [13]). However, none of the control subjects had arteriolar hyalinosis lesions of comparable severity to those observed in the patients categorized in group III because of vascular changes.

Discussion

In IDDM patients with long disease duration (≥ 10 years) and overt nephropathy, non-diabetic renal disease is rare (Mauer M, unpublished data). Thus, in the vast majority of long-term IDDM patients, the loss of kidney function is related to a well-defined pattern of diabetic nephropathology, including glomerular basement membrane and tubular basement membrane thickening and mesangial expansion, especially matrix accumulation, but also arteriolar hyalinosis affecting both afferent and efferent glomerular arterioles [9–15]. Interstitial fibrosis is frequently present, especially in patients with advanced glomerulopathy and typically in areas with global glomerular sclerosis and tubular atrophy [11, 13]. This pattern of renal lesions is quite monotonous and predictable in IDDM patients with clinical nephropathy.

Three studies have reported that non-diabetic renal disease is quite frequent in NIDDM patients with overt nephropathy. Parving et al. [16] found that 1 of 4 of such patients had renal diseases other than diabetes; Gambara et al. [17] confirmed these

data reporting that only 1 of 3 of NIDDM patients with overt nephropathy had typical patterns of DN. Khan et al. [33] recently observed the presence of non-diabetic renal disease in 42 % of 153 NIDDM patients with overt nephropathy; the occurrence of non-diabetic renal disease was much lower (12 %) in the series of 33 proteinuric patients studied by Olsen and Mogensen [34]. In all these studies, however, patients were referred to the nephrologist and kidney biopsies were not performed on the basis of research protocols, but for clinical indications. Thus, these studies do not describe the usual NIDDM patients with nephropathy, but those with an unusual clinical course; also the different results may reflect differences in the criteria for kidney biopsy. A large autopsy study on NIDDM patients did not confirm a high incidence of non-diabetic renal diseases [18]. Thus, the available data on renal structure in NIDDM patients with proteinuria are still inconclusive.

Microalbuminuria in NIDDM has been shown to predict mortality, mainly cardiovascular [22, 24, 25] and, in approximately 20 % of patients, the development of overt proteinuria [23]. However, whether the raised urinary albumin excretion is an expression of underlying diabetic renal lesions is still unknown. Only one study to date evaluated renal structure in microalbuminuric NIDDM patients [35]; surprisingly these authors, who reported diagnostic heterogeneity in proteinuric NIDDM patients [17], found that all 16 microalbuminuric NIDDM patients had classic lesions of diabetic glomerulopathy.

Since 1992 we have been performing kidney biopsies on the basis of a research protocol rather than clinical indications. The present paper summarizes the preliminary analysis in the microalbuminuric patients studied to date.

The initial reading of the light microscopy tissue of these NIDDM patients made apparent the inadequacy of current descriptive formulations, largely based on observations of research biopsies in IDDM (of which the authors have reviewed several hundreds). Virtually all IDDM patients with at least 10 years of diabetes and overt nephropathy have obvious diabetic glomerulopathy. Diabetic glomerulopathy, although less severe, is usually quite advanced in microalbuminuric IDDM patients. We recently reported that all IDDM patients with AER over 30 μg/min had electron microscopic morphometric measures of diabetic glomerulopathy above the normal range [32]. Since electron microscopic morphometric analysis has not been completed in these patients, it is currently impossible to make any precise comparison between diabetic glomerulopathy in IDDM and NIDDM microalbuminuric patients. Nevertheless, many NIDDM patients with microalbuminuria did not have glomerulopathy, or they had very mild mesangial expansion by light microscopy. Thus, 70 % of the microalbuminuric NIDDM patients had normal or near normal glomerular structure by light microscopy, with or without tubulo-interstitial and arteriolar changes. The remaining 30 % had renal changes typical of DN in IDDM, with glomerular, tubulo-interstitial and vascular lesions occurring in parallel.

Thus, we developed a new classification system which included three major groups. Category I was defined as normal or near-normal renal structure, category II as "typical" patterns of renal injury (similar to the changes in IDDM). Category III was defined as "atypical" patterns of renal injury, including severe tubulo-interstitial and/or arteriolar hyalinosis and/or global glomerular sclerosis lesions in the presence of absent or mild glomerular changes.

Thus, despite comparable renal function, NIDDM patients with microalbuminuria are structurally heterogeneous: only 29 % had "typical" DN, 29 % had near normal renal structure and 42 % severe tubulo-interstitial and/or vascular lesions disproportionate to the mild glomerular involvement. In this series of patients we did not find cases of any definable non-diabetic renal disease. The difference between our findings and those in previous reports in proteinuric NIDDM patients (see above) may be explained by the study design, in that patients in the present study had kidney biopsies performed on the basis of a research protocol as opposed to clinical indication for atypical course.

The "atypical" patterns of renal injury observed in many of our patients are probably related to hyperglycaemia, since HbA_{1c} levels were higher both in patients with "typical" and with "atypical" patterns of lesions compared to patients without lesions. Thus, hyperglycaemia may cause different patterns of renal injury in older NIDDM compared to younger IDDM patients. The tubulo-interstitial and vascular changes could also be related to aging and systemic hypertension. However, hypertension was present in almost all patients (except for 3) in all 3 structural categories, and "per se" cannot account for the different lesions observed in category III. Further, mean age was similar in category II and III patients, despite the different patterns of renal injury in the two groups. Also, we examined a large number of age-matched normal control subjects and found that severe lesions, as observed in NIDDM patients, were uncommon in the non-diabetic subjects. Nevertheless, aging and blood pressure may have varying impact in different patients, and therefore may contribute, in presence of other factors, to renal injury in this subset of patients.

The reasons why the kidney may react differently to hyperglycaemia in different patients with NIDDM are not clear. It can be hypothesized that the heterogeneity in renal structure might reflect the heterogeneous nature of NIDDM "per se". Patients with "typical" DN lesions had the longest known diabetes duration, worse metabolic control and they all had

diabetic retinopathy; interestingly their BMI only slightly exceeded normal values, as opposed to clearly increased BMI values in categories I and III.

The nature of this interrelationship of diabetic milieu and renal structural changes remains enigmatic; however, these relationships also extend to diabetic retinopathy. Diabetic retinopathy was present in all C II patients, background in 50 % and proliferative in 50 %. None of the patients in C I and C III had proliferative retinopathy, while background diabetic retinopathy was observed in 50 % of C I and 57 % of C III patients. Thus, all C II patients had diabetic retinopathy and all patients with proliferative retinopathy had "typical" DN.

A high proportion of microalbuminuric NIDDM patients (29 %) had normal or near-normal renal structure. They tended to be younger and had shorter diabetes duration and better metabolic control than patients with renal lesions (categories II and III). Although we do not have an explanation for the abnormal AER in these patients, it is possible that microalbuminuria in this subset is a clinical manifestation of generalized endothelial dysfunction rather than of renal damage "per se". Parving et al. [16] observed what they termed "minimal lesion" nephropathy in 4 of 36 NIDDM patients with clinical proteinuria. It is possible that the patients diagnosed as having "minimal lesion" nephropathy in this latter study are similar to our category I patients, however this will require longitudinal studies to be addressed. Suffice it to say here that a substantial proportion of NIDDM patients with microalbuminuria or proteinuria may have increased glomerular capillary wall permeability to protein for reasons not currently understood.

In summary, in this unselected series of 34 cases biopsied for research reasons, NIDDM patients with microalbuminuria do not have non-diabetic renal diseases; however they may have different patterns of renal injury compared to IDDM patients. More "typical" diabetic nephropathy patterns are seen among microalbuminuric NIDDM patients with proliferative retinopathy and normal BMI, while "atypical" patterns of renal injury are more common among those with increased BMI and background or no retinopathy. Finally, a subset of microalbuminuric NIDDM patients have near-normal renal structure by light microscopy; in these patients the increased renal permeability to protein might be expression of generalized endothelial dysfunction.

Long-term longitudinal studies are needed to determine the course of renal function in these patients with different patterns of renal injury.

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