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Prevalence and causes of albuminuria in non-insulin-dependent diabetic patients

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Prevalence and causes of albuminuria in non-insulin-dependent diabetic patients. A prospective study of the prevalence and causes of persistent albuminuria (>300 mg/24 hr) was conducted in non-insulin-dependent diabetic (NIDDM) patients, age <66 years, attending a diabetic clinic during 1987. All eligible patients ($N = 370$) were asked to collect at least one 24-hour urine sample for albumin analysis. Urine collection was obtained in 224 males and 139 females (98%). Fifty patients (7 women) suffered from persistent albuminuria (13.8%). The prevalence of albuminuria was significantly higher in males (19%) than in females (5%). A kidney biopsy was performed in 35 patients (70%). The kidney biopsies revealed diffuse and/or nodular diabetic glomerulosclerosis in 27 patients (77%), while the remaining eight patients (23%) had a variety of non-diabetic glomerulopathies, such as minimal lesion and mesangioproliferative glomerulonephritis. Diabetic retinopathy was present in 15 of 27 patients (56%) with diabetic glomerulosclerosis, while none of the eight patients with a non-diabetic glomerulopathy had retinopathy. Our cross sectional study has revealed a high prevalence of albuminuria and of non-diabetic glomerulopathy as a cause of this complication in NIDDM patients. Presence of diabetic retinopathy strongly suggests that a diabetic glomerulopathy is the cause of albuminuria. Albuminuric non-insulin-dependent diabetic patients without retinopathy require further evaluation, that is, kidney biopsy.

Thirty to 40 percent of all diabetics, whether insulin-dependent or not, develop persistent proteinuria [1–4]. Persistent proteinuria is the hallmark of diabetic nephropathy which can be diagnosed clinically if the following additional criteria are fulfilled: presence of diabetic retinopathy and no clinical or laboratory evidence of kidney or renal tract disease other than diabetic glomerulosclerosis [5, 6]. The validity of this clinical definition of diabetic nephropathy is well established in insulin-dependent diabetic (IDDM) patients [5, 6], while we are still lacking confirmation in non-insulin-dependent diabetic (NIDDM) patients. Furthermore, the prevalence of non-diabetic renal lesions has been reported much higher in selected series of proteinuric NIDDM patients (about 30%) as compared with proteinuric IDDM patients (approximately 5%) [5, 7–9]. This heterogeneity may explain why there is considerable variation in the natural history and clinical course of so-called "diabetic nephropathy" in NIDDM patients [10].

The aim of our prospective study was to determine the prevalence and causes of persistent albuminuria (>0.3 g/24 hr) in NIDDM patients below 66 years of age. Kidney biopsies were performed in all eligible proteinuric NIDDM patients.

Methods

Patients

In a recent cross sectional study of all (139 females and 224 males) non-insulin-dependent diabetic patients less than 66 years of age, attending Hvidöre Hospital during 1987, we identified 50 patients (seven women) with persistent albuminuria (≥300 mg/24 hr) [11]. Persistent albuminuria was defined as urinary albumin excretion ≥300 mg/24 hr in at least three consecutive, sterile, non-ketotic 24-hour urine samples. Diabetic patients were regarded as suffering from non-insulin-dependent diabetes if they were treated by diet alone, or diet combined with oral hypoglycemic drugs, or if they were treated with insulin and had an onset of diabetes after the age of 40 and a body weight in excess of the ideal body weight at the time of diagnosis [12]. Insulin treated lean patients (<100% ideal body weight) had a glucagon test performed, and non-insulin-dependent diabetes was diagnosed if the stimulated C-peptide value was ≥0.60 pmol/ml [12]. The glucagon/C-peptide test was carried out after an overnight fast. Blood samples for plasma C-peptide determination were obtained before and six minutes after an intravenous bolus injection of 1 mg glucagon (Novo Nordisk, Bagsvaerd, Denmark) as described previously [13].

All 50 proteinuric patients were referred to the departments of nephrology for further examination, except six patients who did not want further evaluation. Two patients did not attend, and kidney biopsy could not be performed due to: anticoagulant treatment in two patients, and a solitary kidney in four patients [nephrectomy ($N = 2$), aplasia ($N = 2$)]. A renal biopsy was performed in the remaining 36 patients.

Methods

Albuminuria was determined by radioimmunoassay with a single antibody [14]. Sterility of urine was checked by quantitative culture. If bacterial growth was found, urine collection was repeated after treatment. Microscopic examination of the urinary sediment was performed in a midstream specimen in all patients with persistent albuminuria. Eight ml of urine was centrifuged at 1500 rpm for five minutes. The supernatant was removed, and resuspended sediment (approximately 0.15 ml)

Table 1. Clinical data in 35 non-insulin-dependent diabetic patients with persistent albuminuria

	Glomerulopathy		*P* value
	Diabetic	Non-diabetic	
Number, sex	1 F/26 M	1 F/7 M	
Age *years*	55 ± 9	56 ± 8	
Body mass index kg/m^3	30.7 ± 5.5	30.6 ± 3–6	
Anti-diabetic treatment (diet/oral hypoglycemic agent/insulin) %	15/55/30	38/62/0	
Hemoglobin A_{1c} %	8.7 ± 2.0	9.4 ± 1.5	
Known duration of diabetes *years*	10 (1–27)	8 (3–9)	
Interval between onset of diabetes and albuminuria *years*	6 (0–17)	0 (0–5)	<0.05
Urinary albumin excretion[a] rate *g/24 hr*	1.9 (0.2–11.4)	1.4 (0.9–3.9)	
Glomerular filtration rate *ml/min · 1.73 m^2*	69 ± 30 (24–146)[b]	96 ± 23 (43–120)[b]	<0.05
Systolic blood pressure *mm Hg*	162 ± 20	136 ± 7	<0.001
Diastolic blood pressure *mm Hg*	91 ± 11	84 ± 9	
Prevalence of hypertension %	89	88	
Retinopathy (proliferative/simple/nil) %	22/37/41	0/0/100	<0.005
Autonomic neuropathy %	74	13	<0.005
Microscopic hematuria %	15	0	

[a] Some patients with nephropathy receiving antihypertensive treatment had albuminuria below 0.3 g/24 hr
[b] Range

was examined on a slide with phase-contrast microscopy. Significant hematuria is defined as three or more erythrocytes per high power field urinalysis of two or more sterile urine samples. Glomerular filtration rate (GFR) was measured in all patients, using a single intravenous injection of 100 μCi ^{51}Cr-EDTA at 9 a.m., with determination of plasma radioactivity in venous blood samples taken 180, 200, 220 and 240 minutes after the injection [15].

Arterial blood pressure was measured three times in the sitting position after 10 minutes of rest. The measurements were carried out with an automatic electronic device (Takeda Medical UA-751, Tokyo, Japan), cuff size 25 × 12 cm in lean adults and 30 × 15 cm in obese patients. Arterial hypertension was diagnosed according to the World Health Organization's criteria (≥160/95 mm Hg) or if antihypertensive treatment was being prescribed. Hemoglobin A_{1c} (DIAMAT Analyzer, BIO-RAD, California, USA) was determined. Normal range for HbA_{1c} was 4.1 to 6.1%. Ophthalmoscopy and fundus photography (Canon CFD-60Z, Kawasaki, Japan) through dilated pupils were carried out in all patients. Autonomic neuropathy was diagnosed if beat-to-beat variation in heart rate during hyperventilation was ≤15 beats per min [16]. Body mass index (weight/height^2) was calculated.

A renal biopsy was performed in 36 patients. Insufficient material was obtained in one patient. All biopsies were reviewed by two observers who were unaware of the clinical features.

Light microscopy. The tissue was fixed in 4% formaldehyde buffered to pH 7.0 ("Lillie's fluid"), embedded in Paraplast® (Fisher Company, Fair Lawn, New Jersey, USA) cut into 4, 3 and 2 μm sections and stained with hemotoxylin-eosin, periodic-acid Schiff, picric acid + sirius red Masson's trichrome and silver methenamine + hematoxylin-eosin.

Immunofluorescent microscopy. Kidney specimens were frozen using dry ice, embedded in Tissue-Teck (Miles, Naperville, Illinois, USA) gelatin, and sections of 2 μm were cut at −24°C on a Leitz Histocryotome (Wetzlar, Germany). Direct immunofluorescent staining technique was applied, using FITC-conjugated rabbit or goat antisera specifically reactive to human IgG, IgM, IgA as well as complement C_{1q}, C_3 and C_4 [17].

Electron microscopy. Tissue was available in 24 out of the 35 kidney biopsies. The tissue was fixed in 3% glutaraldehyde at pH 7.4, followed by dehydration in increasing concentrations of ethanol, after fixation in 1% osmium tetroxide, and embedded in Epon. Ultra-thin sections were cut on an LKB I ultramicrotone and examined on a Philips 100 electron microscope.

Light microscopy

Histological classification of the glomerular lesions was according to the World Health Organization standard [18]. The following definition of histological entities was applied:

Diabetic glomerulosclerosis (glomerulopathy): Diffuse. Global and diffuse widening of the mesangial regions with a delicately fibrillar appearance showing radiating finger-like extensions from the glomerular pole (if represented in the glomerular cross section).

Nodular. Mesangial areas with a large central acellular or nearly acellular region surrounded by a rim of nuclei or small extended marginal capillary.

Degree of severity of the diabetic lesions in the glomeruli was estimated (from 1 to 3) by the amount of matrix in mesangium of non-sclerosed glomeruli.

Non-diabetic glomerular lesions: Minimal lesion. Glomeruli were normal or a slight global and diffuse mesangial hypercellularity (a maximum of 4 cell nuclei) associated with negative immunofluorescence and absence of glomerular deposits by electron microscopy.

Mesangioproliferative glomerulonephritis. Global and diffuse mesangial hypercellularity with a number of cell nuclei more than nine in the mesangial segments [19] associated with global and diffuse distribution of immunoglobulins and/or C_3 in the glomeruli [20].

Glomerulonephritis sequelae. Global mesangial widening with fibrous adhesions between some of the capillary loops and the inner side of the capsule of Bowman associated with a diffuse distribution of immunoglobulin and C_3 in the glomeruli.

Statistical analysis

Values are expressed as mean ± SD or median with range in parenthesis. For evaluating frequencies, the chi-squared test was used and for evaluating continuous variables the Mann-Whitney test was used for comparison between the two groups. A P value (two tailed) <0.05 was considered significant.

Results

Our cross sectional study showed a prevalence of albuminuria of 13.8% (50/363 patients). The prevalence of albuminuria was significantly higher in males (19%) than in females (5%), $P < 0.005$.

Table 2. Renal pathology in 35 non-insulin-dependent diabetic patients with persistent albuminuria

Patient no.	Light and electron microscopy				Immunofluorescence microscopy					
					Immune deposits		Localization in glomeruli			
	Diabetic glomerulo-sclerosis	Grading of severity	No. G/S	Non-diabetic glomerular lesions	Immuno-globulins	Complement-fractions	Mesangium	Capillary	Global	Segmental
01	Diffuse	1	17/0	Absent	0	0	−	−	−	−
02	Absent		20/1	GN, sequelae	IgM	0	+	+	+	−
03	Diffuse	2	15/3	Absent	0	0	−	−	−	−
04	Absent		8/1	Min. lesion	0	0	−	−	−	−
05	Nodular	3	17/1	Absent	No tissue					
06	Absent		8/0	Mesangio-prolif. GN	0	C_3	+	+	+	−
07	Nodular	2	10/1	Absent	0	0	−	−	−	−
08	Diffuse	2	35/5	Absent	IgM, IgA	0	+	+	−	+
09	Diffuse	1	15/4	Absent	0	C_3	−	+	−	+
10	Diffuse	1	21/4	Absent	No tissue					
11	Absent		10/1	Min. lesion	0	0	−	−	−	−
12	Absent		22/1	Mesangio-prolif. GN	IgM, IgA	0	+	−	+	−
13	Diffuse	1	24/1	Absent	0	0	−	−	−	−
14	Diffuse	2	22/4	Absent	No tissue					
15	Diffuse	2	40/25	Absent	0	0	−	−	−	−
16	Diffuse	1	8/1	Mesangio-prolif. GN	IgM, IgA	C_3	+	+	+	−
17	Diffuse	2	10/2	Absent	No tissue					
18	Absent		4/0	Min. lesion	0	0	−	−	−	−
19	Absent		12/1	Min. lesion	0	0	−	−	−	−
20	Nodular	2	53/23	Absent	0	0	−	−	−	−
21	Nodular	3	16/7	Absent	IgG, IgA	0	+	+	−	+
22	Diffuse	1	15/2	Absent	IgM, IgA	0	+	+	+	+
23	Diffuse	2	22/14	Absent	0	C_3	+	+	−	+
24	Nodular	2	8/2	Absent	No tissue					
25	Nodular	2	15/6	Absent	IgG, IgM	0	−	+	−	+
26	Diffuse	1	33/3	Absent	IgM, IgA	C_3	+	+	−	+
27	Diffuse	2	10/0	Absent	0	0	−	−	−	−
28	Diffuse	1	13/4	Absent	IgM	C_{1q}	+	+	−	+
29	Diffuse	1	10/0	Absent	0	0	−	−	−	−
30	Nodular	3	4/2	Absent	No tissue					
31	Diffuse	1	17/7	Absent	No tissue					
32	Diffuse	1	51/3	Absent	IgM	0	+	+	+	−
33	Nodular	3	18/12	Absent	IgM	C_3	+	+	−	+
34	Diffuse	1	7/0	Absent	IgG, IgM	C_3	+	+	−	+
35	Diffuse	1	48/0	Absent	0	0	−	−	−	−

Abbreviations are: G, glomeruli; S, sclerosed; Min., minimal; GN, glomerulonephritis; Mesangioprolif., mesangioproliferative. Slight = 1, medium = 2, severe = 3.

A kidney biopsy was performed in 35 of the albuminuric patients and their clinical characteristics and pertinent laboratory findings are shown in Table 1. There were no significant differences in sex, age, body mass index, anti-diabetic treatment, hemoglobin A_{1c}, known duration of diabetes, or prevalence of hypertension between proteinuric patients with or without diabetic glomerulopathy. The majority of patients with a non-diabetic glomerulopathy had albuminuria already at the time of diagnose of diabetes. Lack of retinopathy and a low prevalence of autonomic neuropathy also characterized these patients. Diabetic glomerulosclerosis was found in all (N = 15) our albuminuric diabetic patients suffering from diabetic retinopathy. Thus, the diagnostic specificity (predictive value of a positive test) of retinopathy is 100% (15/15) while the diagnostic sensitivity (predictive value of a negative test) is only 40% (8/20). Forty-one percent of our patients with biopsy proven diabetic glomerulopathy lacked diabetic retinopathy. Four patients with diabetic glomerulosclerosis and well-preserved kidney function (GFR: 45, 51, 55 and 100 ml/min/1.73 m^2) had persistent hematuria.

The histological findings, deposits of immunoglobulins and complement fractions and their localization are shown in Table 2. Nineteen patients had a diffuse diabetic glomerulosclerosis and eight suffered from a nodular diabetic glomerulosclerosis. One patient had a mesangioproliferative glomerulonephritis superimposed on a diffuse diabetic glomerulosclerosis. Four patients had minimal lesion nephropathy, two patients suffered from mesangioproliferative glomerulonephritis, and one patient had sequelae after a glomerulonephritis.

Discussion

Our cross sectional study showed a prevalence of albuminuria of 13.8% in NIDDM patients less than 66 years of age. The prevalence of persistent albuminuria was four times higher in males than in females. Histological examinations demonstrated

that non-diabetic glomerulopathies accounted for approximately one quarter of all our cases with persistent albuminuria. These patients were characterized clinically by: lack of retinopathy, low prevalence of autonomic neuropathy, and a short time interval between onset of diabetes and of albuminuria.

Since our study was not a survey based on the general population, selection bias might have been a confounding variable. Selective referral cannot be excluded, since 30% of our patients had albuminuria at the time of referral. However, the prevalence of albuminuria in relation to known duration of NIDDM is practically identical with the results obtained in two surveys based on a general population revealing a prevalence of albuminuria of 12% and 15%, respectively [21, 22]. We have no evidence suggesting that the patients who dropped out were unrepresentative of the group as a whole except those with albuminuria (excess mortality).

The male predominance of proteinuric patients was more marked in the present study as compared to previous investigations [4, 21, 22]. A male predominance has also been documented in proteinuric IDDM patients [1, 2]. The prevalence of non-diabetic kidney diseases in proteinuric NIDDM patients is approximately 30% [7–9]. This finding is based on retrospective studies of kidney biopsy specimens. In all three studies renal biopsy was performed because of abnormal urine sediment, particularly increased number of erythrocytes or casts, lack of retinopathy, or other findings inconsistent with either the clinical expression or the natural history of diabetic nephropathy. These selection criteria will lead to an overestimation of the real prevalence of non-diabetic kidney diseases in proteinuric NIDDM patients. This suggestion is supported by the finding of a lower prevalence (23%) of non-diabetic glomerulopathies in our prospective study, where no special selection criteria were applied. The prevalence of non-diabetic kidney diseases in proteinuric IDDM patients is approximately 5% [5]. The discovery of a non-diabetic kidney disease in a proteinuric diabetic patient may have an effect on the prognosis and may alter the therapy for the renal disease. However, no alteration in therapy was performed in our study.

Forty-one percent of our proteinuric NIDDM patients with biopsy-proven diabetic nephropathy lacked diabetic retinopathy as compared to 62% and 60% of the proteinuric NIDDM patients studied by Marshall and Alberti [23] and Schmitz and Vaeth [24]. These findings are remarkable compared to IDDM patients, where only a few percent of the proteinuric patients are without retinopathy [25]. The mechanisms involved are unknown. But special local conditions in the renal cortex must prevail in order to account for the more accelerated development of microangiopathy in the kidney as compared to the retina in NIDDM patients with diabetic nephropathy. Hemodynamic factors may well play a role, since several of the age induced alterations in the kidney, such as nephron loss and arteriolar hyalinosis causing impairment of the renal autoregulation, can lead to a condition with elevated glomerular hydraulic pressure. The high prevalence of systemic hypertension in the elderly NIDDM patients may further aggravate this condition [11].

Recently, Grenfell et al [26] have suggested that diabetic nephropathy can be diagnosed clinically in NIDDM patients if they have persistent proteinuria, diabetic retinopathy and no clinical or laboratory evidence of kidney or renal tract disease other than diabetic glomerulosclerosis. We have confirmed this suggestion by demonstrating that all our proteinuric NIDDM patients with diabetic retinopathy had diabetic glomerulosclerosis as the cause of albuminuria. On the other hand, lack of retinopathy is a poor predictor of a non-diabetic kidney disease, which is in contrast to the suggestion made in the past [26]. Albuminuric NIDDM patients without retinopathy require further evaluation, that is, kidney biopsy, since the chance for a diabetic or non-diabetic glomerulopathy is approximately fifty-fifty.

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