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Different types of proteinuria in diabetes mellitus

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Urinary protein concentration and urinary protein pattern as determined by sodium dodecyl sulphate polyacrylamide gel electrophoresis, were investigated in 53 type 1 diabetic children and in 56 (41 type 1 and 15 type 2) diabetic adults. Reversible tubular proteinuria was found in 26 diabetic children with hyperglycaemic ketoacidosis. Among the patients, 43 exhibited physiological, 31 fixed tubular and nine glomerular type proteinuria. The prevalence of retinopathy and neuropathy in the different patient groups has also been evaluated. Urinary protein concentration appeared to be above the usual reference values during hyperglycaemic ketoacidosis, and was normalized with the successful control of metabolism. In the other three groups, urinary protein concentration was increased only in the case of glomerular type proteinuria. It is suggested that the above classification characterizes the development of diabetic nephropathy, progressing from reversible tubulointerstitial dysfunction through fixed tubulointerstitial dysfunction to glomerulopathy.

In recent decades attention has shifted from the acute metabolic derangements of diabetes mellitus to its late consequences. Diabetic nephropathy has a devastating effect on survival, particularly in diabetics of youthful onset and therefore mainly, though not exclusively, in insulin dependent patients [1]. Yet we are still faced with the puzzling phenomenon that clinically significant diabetic renal disease develops in about one third of juvenile onset diabetics [7] and at present there are no means to predict which diabetic will develop glomerulosclerosis [13].

Demonstrable renal abnormality occurs early in the course of diabetes, in the first months, weeks or even days after the clinical onset of the disease. The two phenomena which have attracted most attention in this early phase are hyperfiltration, in other words a raised glomerular filtration rate, and generalized kidney enlargement [6, 9].

Diabetic kidney disease is primarily a glomerulopathy and the earliest clinical hallmark of advanced diabetic nephropathy is a glomerular proteinuria.

According to most authors an important phase of incipient diabetic nephropathy is evidenced by a 10 to 20 fold or even smaller increase in baseline albumin excretion aggravated during the exercise provocation test [10]. Others, however, have reported increased tubulary microprotein excretion in insulin dependent

diabetes of 1–10 years duration, and concluded that tubular proteinuria might be the first marker of diabetic nephropathy [8, 12].

In view of these data the aim of the present study was to determine the degree and type of proteinuria in diabetic patients of different ages and with different duration of the disease.

Materials and Methods

Two groups of patients were investigated.

The first group included 53 insulin dependent juvenile diabetics (33 girls and 20 boys) aged 2–16 years. The duration of the disease ranged from 0 to 11 years. 26 children were suffering from hyperglycaemic ketoacidosis and the remaining 27 patients were having a good overall metabolic control at the time of investigation.

The other study population consisted of 56 diabetic patients (21 females and 35 males) between 19 and 68 years of age. The duration of the disease ranged from 1 to 32 years. Of the patients 41 had type 1 and 15 type 2 diabetes. Symptoms of retinopathy occurred in 30 patients and neuropathy in 15 patients. All diabetics included in this group exhibited a good metabolic control.

In most patients a 24 h urine specimen was collected, but in children with hyperglycaemic ketoacidosis only individual fractions were evaluated. Neutral phosphate buffer and sodium azide were added to the urine to reach a final concentration of 0.05 mmol/l and 0.05% respectively. After filtration the samples were stored at −20 °C.

Urinary protein concentration (UPC) was measured according to the method of Yatzidis [15]. Determination of urinary protein pattern (UPP) was carried out by sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS PAGE) [2, 5].

The various proteins separated on the gel were grouped as follows (1) High molecular weight (HMW) globulins of 1,000,000–100,000 molecular weight; (2) middle molecular weight proteins mainly consisting of albumin and transferrin; (3) low molecular weight (LMW) microproteins of 60 000–12,000 molecular weight.

Table I

UPC and UPP of patients with different types of proteinuria

No. of patients	Type of proteinuria	UPC mg/l	UP patterns relative per cent		
			HMW	MMW	LMW
		Mean range	Mean range	Mean range	Mean range
26	Reversible tubular in coma	279 77–650	8.5 1.0–15.6	50.4 25.1–69.1	41.1 19.8–69.8
	after coma	165 95–350	9.1 1.0–25.7	77.3 62.2–98.0	13.6 1.0–29.0
43	Physiological	191 75–380	5.4 0.2–15.4	83.9 64.0–98.0	10.8 0–25.8
31	Fixed tubular	183 45–1000	5.6 0–13.3	49.3 27.2–69.3	45.1 26.2–72.1
9	Glomerular	2400 145–5100	14.2 10.3–22.0	82.4 66.4–89.3	3.4 0–16.6

Results

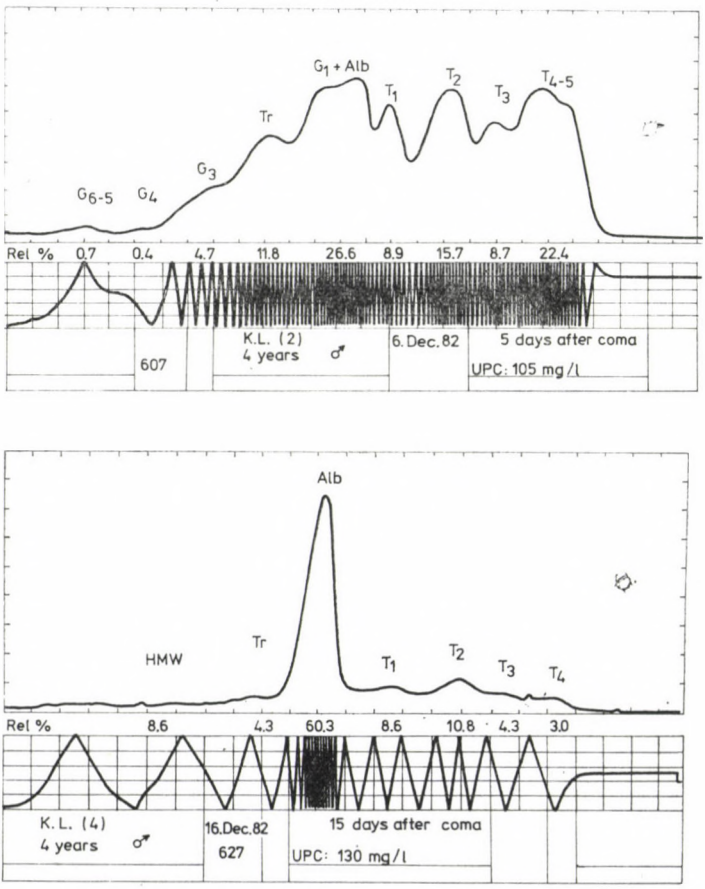
The following types of proteinuria were observed:

(i) Reversible tubular proteinuria
(ii) physiological proteinuria
(iii) fixed tubular proteinuria
(iv) glomerular proteinuria

Table I shows UPC and UPP of patients with different types of proteinuria.

Ad *(i)*. In all the children suffering from hyperglycaemic ketoacidosis severe tubular proteinuria was found regardless of whether the metabolic disturbance had been the first manifestation of the disease, or else a disturbance of metabolism that occurred after 0.5 to 11 years of insulin dependent diabetes. In all cases tubular proteinuria appeared to be reversible, turning into physiological proteinuria within a short period of 5 days to 8 weeks (Figs 1–2).

Ad *(ii)*. In 43 patients physiological proteinuria occurred with a good



Figs 1 and 2 Urinary protein pattern of a 4-year old patient, 5 days and 15 days after an episode of hyperglycaemic ketoacidosis

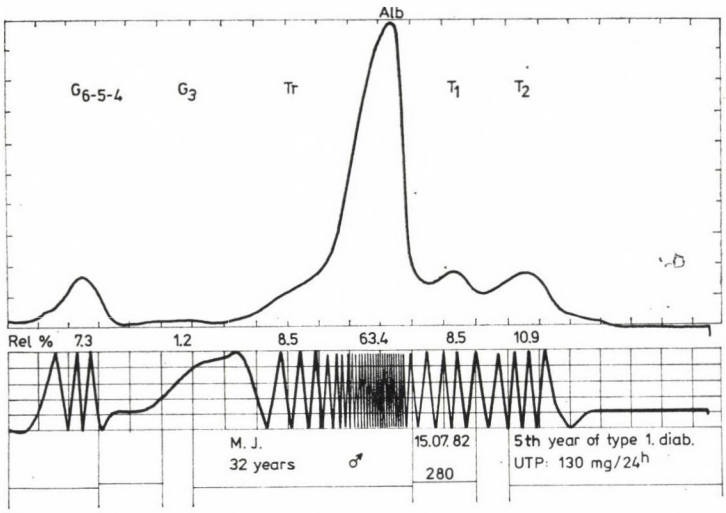


FIG. 3. Urinary protein pattern of a 32 years old diabetic. Physiological proteinuria

overall metabolic control even in the presence of retinopathy (8 cases) and neuropathy (6 cases) (Fig. 3). All the children with a good metabolic condition exhibited physiological proproteinuria.

Ad *(iii)*. Fixed tubular proteinuria occurred in 31 patients having a good metabolic control. Among them 14 had retinopathy and 12 neuropathy. As it has been observed before, the frequency of fixed tubular proteinuria increases with the duration of diabetes [12] (Fig. 4).

Ad *(iv)*. Non-selective glomerular proteinuria was observed in nine patients (Fig. 5). There was no difference in the last two groups in terms of age and the duration of diabetes, but retinopathy occurred in

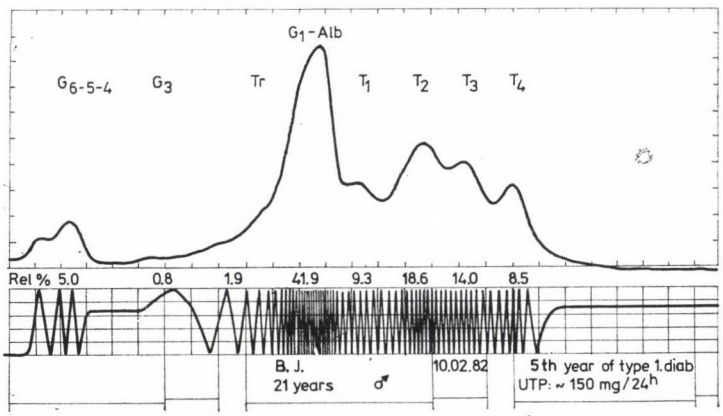


FIG 4. Urinary protein pattern of a 21 years old diabetic. Fixed tubular proteinuria

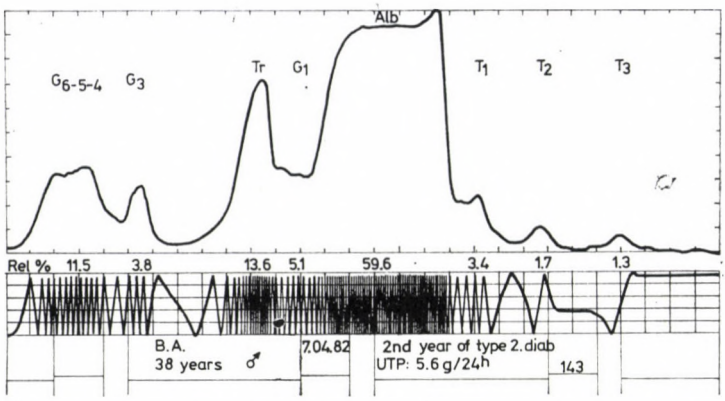


FIG. 5. Urinary protein pattern of a 38 years old diabetic. Glomerular proteinuria

nine and neuropathy in five out of nine patients.

During hyperglycaemic ketoacidosis UPC was above the usual reference values [5], although it became normal after coma. In groups with physiological and fixed tubular proteinuria UPC exhibited normal or near normal values. In patients with glomerular proteinuria an increased UPC was found.

Table II summarizes the clinical data of patients with different types of proteinuria. It is seen that the prevalence of retinopathy and neuropathy increased with physiological proteinuria through fixed tubular proteinuria to glomerular proteinuria.

DISCUSSION

Definitive diabetic nephropathy is a glomerulopathy. The main features of diabetic glomerulopathy are destruction of the basement membrane and proliferation-hyalinization [14].

Analysis of the proteinuric pattern reflects the involvement of different nephron parts in the course of diabetic nephropathy. Tubular proteinuria is a marker of tubulointerstitial insufficiency. The present results suggest that even recent onset diabetics develop tubular proteinuria during acute metabolic disturbances. Proteinuria occurring in hyperglycaemic ketoacidosis in short term diabetes appears,

TABLE II

Clinical data of patients with different types of proteinuria

Type of proteinuria	Patient No.	Age, yrs	Type of diabetes		Duration of diabetes, yrs	Sex		Retinopathy	Neuropathy
			type 1	type 2		M.	F.		
Reversible tubular	26	2.5–15.5	26	—	0–11	8	18	—	—
Physiological	43	2–68	38	5	0–22	21	22	8	6
Fixed tubular	31	19–67	23	8	1–30	21	10	14	12
Glomerular	9	38–62	7	2	2–32	5	4	9	5

however, to be reversible with the successful control of metabolism. Thus, the acute tubulointerstitial dysfunction is a reversible condition. Later in the course of diabetic nephropathy the frequency of fixed tubular proteinuria is increasing as shown by the results. We still do not know the exact mechanism of the process, although we suppose that besides individual factors a poor metabolic control, permanent glycosuria and recurrent ketonuria play a major part in the persistence of the tubulointerstitial failure represented by fixed tubular proteinuria.

Non-selective glomerular proteinuria reflects the involvement of glomeruli in the pathologic process. In a minor fraction of the patients there was a definitive glomerulopathy. While the factors leading to destruction of the glomerular structures are still obscure, extreme glucose and ketone loads may play some role in it [3] as extreme phosphate and protein load produces glomerular fibrosis [4].

On the basis of the results, the above classification of proteinuria provides a good characterization of the development of diabetic nephropathy in terms of the proteinuric pattern (Table III).

Some authors suggest that established clinical nephropathy in patients with diabetes may be slowed down, arrested or even reversed by a substantial and prolonged improvement of glycaemic control [11]. Reversible tubular proteinuria, the hallmark of reversible tubulointerstitial failure, arising in hyperglycaemic ketoacidosis even in recent onset diabetic patients might be the earliest sign of the slowly developing diabetic nephropathy. At any rate it will be necessary to follow longitudinally the evolution of proteinuria in patients showing reversible tubular proteinuria in order to correlate the observed changes with the therapeutic control and general metabolic parameters.

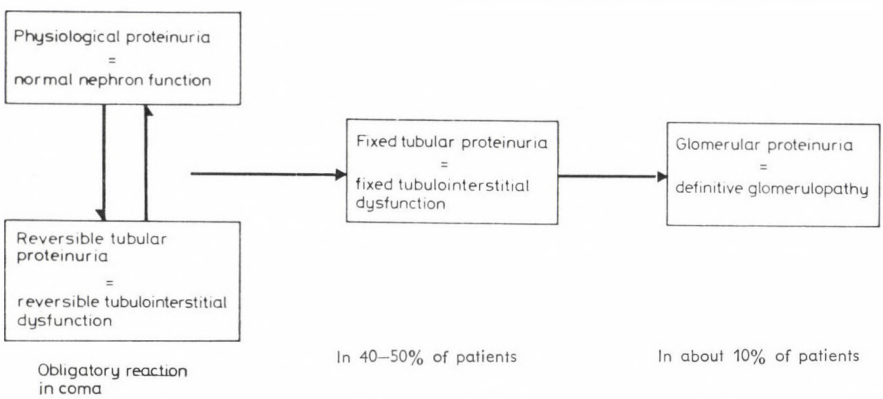


TABLE III

Assumed development of diabetic nephropathy in terms of different types of proteinuria

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