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Monitoring Progression of Diabetic Nephropathy

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ABSTRACT

Glomerular filtration rate (GFR, single bolus ^{51}Cr-EDTA technique), serum creatinine and serum β_2-microglobulin concentrations were measured simultaneously in 49 insulin-dependent diabetics with diabetic nephropathy. GFR ranged from 148 to 23 ml/min/1.73 m^2. Inverse serum concentrations of creatinine and β_2-microglobulin showed a significant correlation with GFR over the whole range of values, $r = 0.87$ and $r = 0.90$, respectively ($p < 0.001$). In the 31 patients with a GFR < 80 ml/min/1.73 m^2, serum concentration of creatinine and β_2-microglobulin were within the normal range in 12 and 9 patients, respectively. With GFR below 60 ml/min/1.73 m^2, all patients had elevated serum β_2-microglobulin concentrations, while 24% of the patients still had normal creatinine concentration. Linear regression analysis between log GFR and log serum β_2-microglobulin showed a better relationship than between log GFR and log serum creatinine, slope -0.90 and -0.57, respectively, $p < 0.01$. A prospective study for up to 70 months was performed in 18 of the patients. The study showed a closer relationship between the individual rate of decline in log GFR and log serum β_2-microglobulin compared to log GFR versus log serum creatinine, $p < 0.01$. Neither serum creatinine nor serum β_2-microglobulin can be used as methods for screening of early impairment of renal function (GFR < 80 ml/min/1.73 m^2 in diabetic nephropathy. Our study suggests that serum β_2-microglobulin is more ideal endogenous marker for GFR estimation than serum creatinine. The accuracy and precision of serum β_2-microglobulin is better than serum creatinine in monitoring the individual rate of decline in kidney function in diabetic nephropathy.

Key words: Diabetic nephropathy, glomerular filtration rate, insulin-dependent diabetes mellitus, serum creatinine, serum β_2-microglobulin.

Determination of serum creatinine is probably the most commenly used method for estimation of glomerular filtration rate (GFR). The disadvantages of serum creatinine are well known (9). Originally, Wibell et al. (14). suggested that measurements of serum β_2-microglobulin concentration might be more useful than

serum creatinine for detection of a slightly reduced GFR. Recent studies in diabetic nephropathy have suggested that serum β_2-microglobulin is a reliable and sensitive method in screening for early impairment of GFR (16,15,3).

The aim of our crossectional study was to evaluate this suggestion by measuring simultaneously GFR and serum concentrations of creatinine and β_2-microglobulin. Furthermore, we performed a prospective study of the 3 above mentioned variables to elucidate the usefulness of the serum concentration of creatinine and β_2-microglobulin monitoring the rate of decline in GFR in individual patients.

MATERIAL AND METHODS

Seventeen females (mean age 31 years) and 32 males (mean age 34 years) with insulin-dependent diabetes mellitus (IDDM) and diabetic nephropathy were investigated. All patients were characterized by persistent proteinuria (>0.5 g/24 h), serum creatinine less than 250 µmol/l, age less than 50 years, onset of IDDM before the age of 31 years. All patients had diabetic retinopathy. Mean duration of diabetes was 20 years. Diabetic nephropathy was diagnosed clinically according to previously described criteria (11). All patients were insulin-dependent from the time of diagnosis and all recieved 2 daily injections of insulin (mean dose of 0.62 IU/kg/day). Twenty-six patients received antihypertensive treatment (metoprolol, hydralazine and furosemide or thiazide). In addition one patient received phenytoin, 300 mg/day for epilepsy. Apart from IDDM all patients were healthy and free of lymphoproliferative and autoimmune diseases. Urine culture was sterilie in all.

All investigations were made on the same day between 09.00 h and 13.00 h. The patients had their normal breakfast and morning insulin before the investigations, which were carried out with the patients resting in the supine position. All patients were investigated once. In addition, 18 patients were studied 6 to 14 times during an investigation period ranging from 18 to 70 months. GFR was measured after a single intravenous injection of ^{51}Cr-EDTA by studying the plasma disappearance for 4 h (2). The mean intra-individual coefficient of variation for GFR was 4.1%. Serum- and urine creatinine were measured using a time reaction technique which reduces the interference from pseudo-creatinines (6). Serum β_2-microglobulin concentrations were measured by radioimmunoassay (Phadebas, β_2 -micro test, Pharmacia Diagnostics AB, Uppsala, Sweden). The coefficient of variation for creatinine and β_2-microglobulin was 2.2% and 4.6%, respectively within assays and 2.9% and 4.9% between assays. The upper limit of normal for serum creatinine in our laboratory is 100 µmol/l (females) and 120 µmol/l (males). The upper limit of normal for serum β_2-microglobulin in our laboratory is 2.4 mg/l for both

Statistical analysis was performed with the paired student's t-test. The relation between the variables was estimated by linear regression analysis.

RESULTS

Table I and II show that serum concentrations of creatinine and β_2-microglobulin remain within the upper limit of normal in 12 and 9 patients out of 31 patients with a GFR below 80 ml/min/1.73 m^2, respectively.

Table I. Glomerular filtration rate, serum concentration of creatinine and β_2-microglobulin in 32 male patients with diabetic nephropathy

GFR (ml/min/1.73m^2)	Number of male IDDM patients with: Serum creatinine (µmol/l) <120	>120	Serum β_2-microglobulin (mg/l) <2.4	>2.4
>80	11	1	12	0
<80	7	13	7	13

Table II Glomerular filtration rate, serum concentration of creatinine and β_2-microglobulin in 17 female patients with diabetic nephropathy

GFR (ml/min/1.73m^2)	Number of female IDDM patients with: Serum creatinine (µmol/l) <100	>100	Serum β_2 microglobulin (mg/l) <2.4	>2.4
>80	5	1	6	0
<80	5	6	2	9

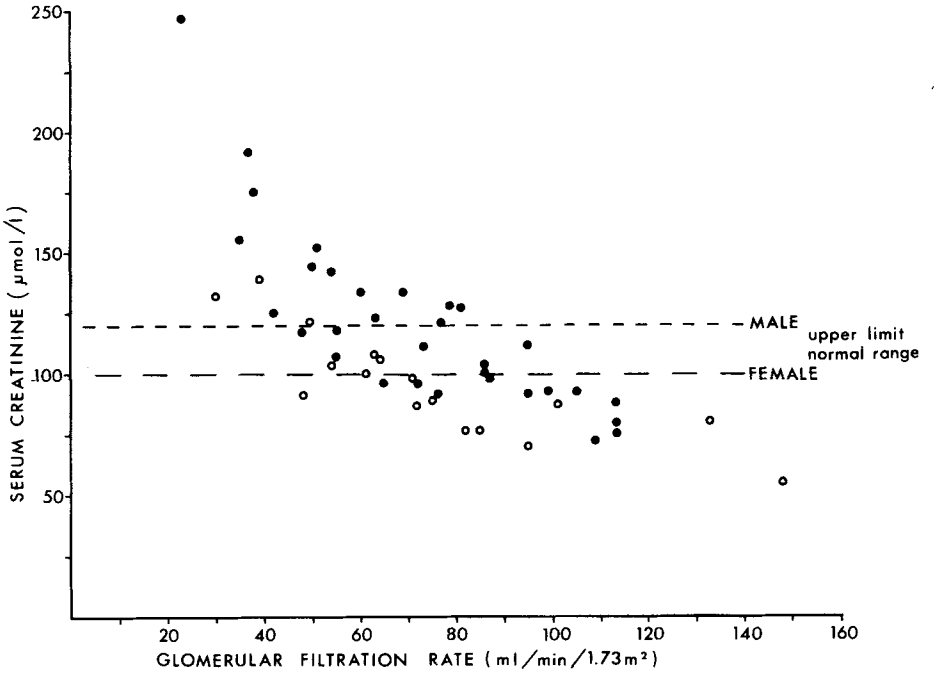

Fig 1. Glomerular filtration rate versus creatinine concentration in 17 females (o) and 32 males (•) with diabetic nephropathy. Broken lines indicate the upper limit of normal range in our laboratory for females and males.

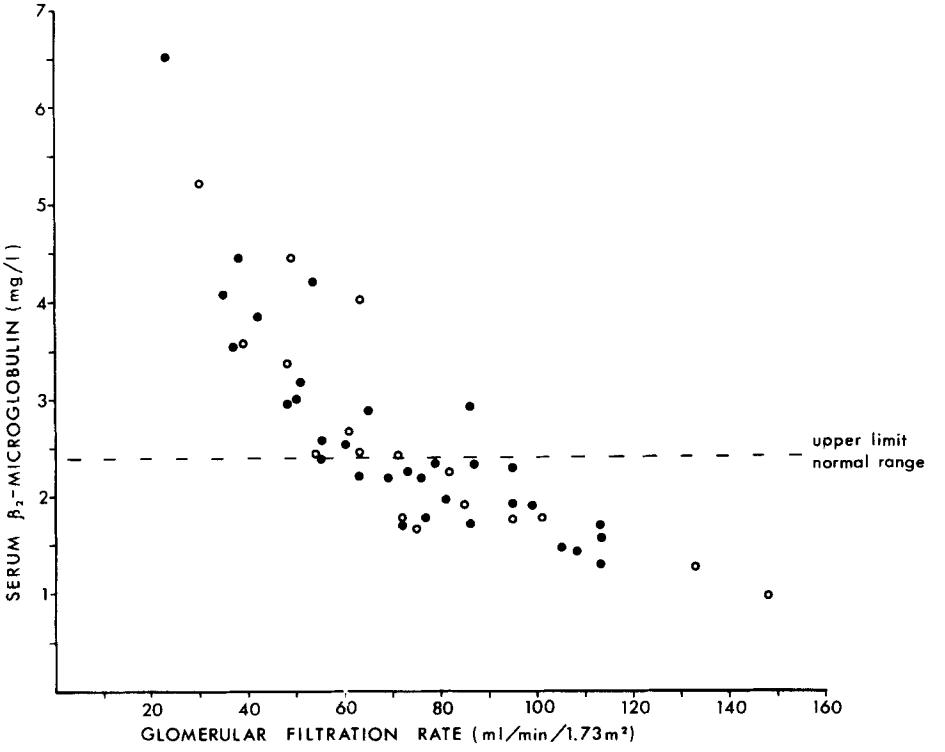

Fig 2. Glomerular filtration rate versus β_2-microglobulin concentration in 17 females (o) and 32 males (•) with diabetic nephropathy. The broken lines indicate upper limit of normal range.

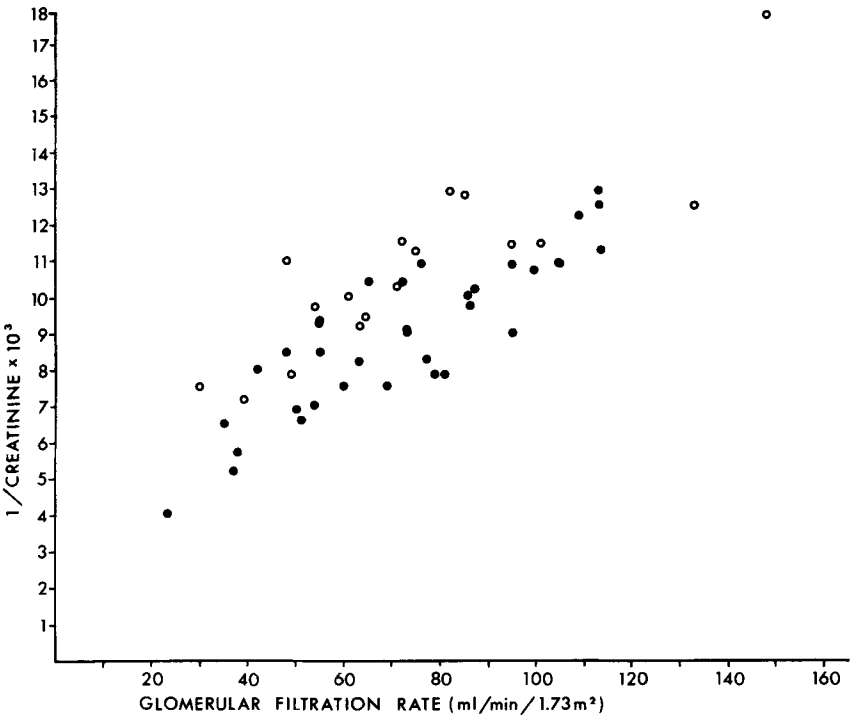

Fig 3. Glomerular filtration rate versus inverse serum creatinine concentration in 17 females (o), r = 0.87, p< 0.01 and 32 males (●), r = 0.88, p<0.001 with diabetic nephropathy.

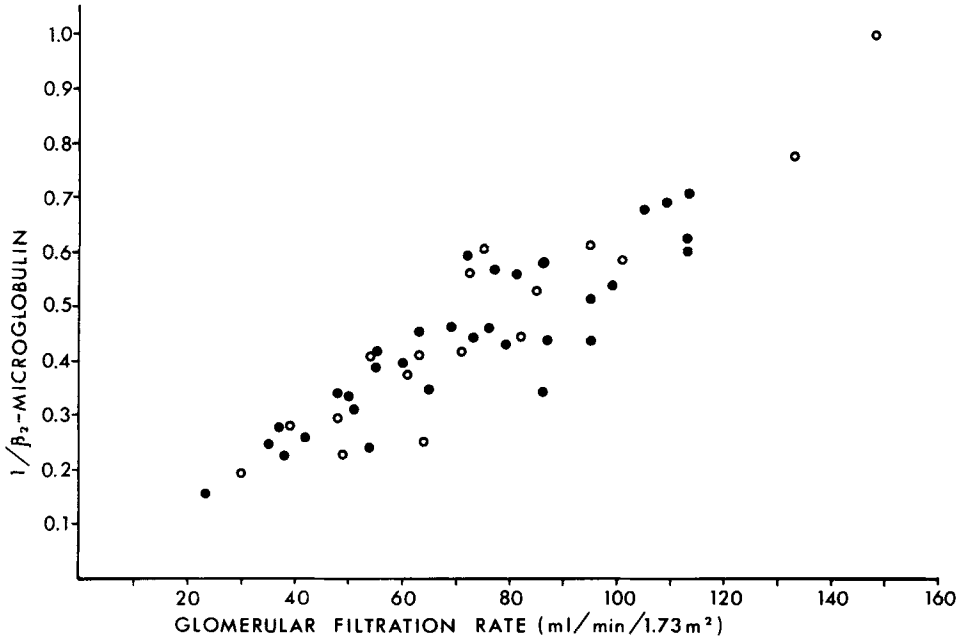

Fig 4. Glomerular filtration rate versus inverse serum β_2-microglobulin concentration in 17 females (o), r = 0.94, p < 0.01, and 32 males (●), r = 0.88, p < 0.001. with diabetic nephropathy.

Figure 1 and 2 show the relationship between serum concentrations of creatinine and β_2-microglobulin on the one hand and GFR on the other. With GFR below 60 ml/min/1.73m^2, all of the serum β_2-microglobulin concentrations exceeded the upper limit of normal, while 24% of the patients (4/17) still had normal serum creatinine concentration. Serum creatinine concentration was normal in 2 patients with a GFR as low as 48 ml/min/1.73 m^2.

Figure 3 and 4 show the correlation between GFR on the one side and inverse serum creatinine values ($r = 0.87$, $n = 17$ females; $r = 0.88$, $n = 32$ males, $p < 0.01$), and inverse serum β_2-microglobulin levels ($r = 0.94$, $n = 17$ females; $r = 0.88$, $n = 32$ males, $p < 0.01$) on the other.

Table III shows that the slope of the regression lines between log GFR versus log β_2-microglobulin is closer to the ideal slope of -1.0 than demonstrated for the relationship between log GFR versus log creatinine. Our longitudinal study of 18 IDDM patients revealed the same results(Table IV).

Table III

Linear regression analysis between log glomerular filtration rate and log serum β_2-microglobulin and log serum creatinine in 49 insulin-dependent diabetics with nephropathy

Subject No	Sex	Slope of the regression lines	
		β_2-microglobulin	creatinine
32	M	-0.842	-0.596
		(0.694-0.990)	(0.481-0.711)
17	F	-1.011	-0.508
		(0.753-1.247)	(0.356-0.660)
49	M+F	-0.90	-0.573
		(0.775-1.023)	(0.459-0.687)

Mean and 95% confidence limits indicated

Table VI

Linear regression analyses between Log glomerular filtration rate and Log serum β_2-microglobulin and Log serum creatinine in 18 insulin-dependent diabetic patients with diabetic nephropathy

Patients	Slope of the regression lines		Correlation coefficient of the regression lines	
	β_2-micro-globulin	creatinine	β_2-micro-globulin	creatinine
1	-1.05	-0.23	-0.96	-0.67
2	-0.73	-0.82	-0.75	-0.71
3	-0.73	-0.42	-0.89	-0.50
4	-1.23	0.15	-0.90	0.23
5	-0.46	-0.27	-0.25	-0.27
6	-1.11	-0.47	-0.91	-0.60
7	-0.80	0.19	-0.89	0.26
8	-0.56	-0.76	-0.03	-0.09
9	-0.51	-0.30	-0.62	-0.41
10	-1.14	-0.42	-0.85	-0.57
11	-0.99	-0.79	-0.96	-0.91
12	-0.44	0.01	-0.59	0.02
13	-0.87	-0.53	-0.94	-0.83
14	-0.87	-0.66	-0.75	-0.94
15	-0.99	-0.95	-0.70	-0.93
16	-0.87	-0.24	-0.93	-0.72
17	-0.34	-0.96	-0.22	-0.60
18	-0.95	-0.95	-0.91	-0.93
Mean	-0.81	-0.47	-0.73	-0.51
+SD	+0.26	+0.37	+0.28	+0.39

DISCUSSION

The major novel information obtained from our prospective study is that the inverse serum β_2-microglobulin concentration can be used as a simple and fairly reliable method for monitoring glomerular function in individual patients with GFR values ranging from 116 to 23 ml/min/1.73 m^2. By contrast our results suggest that the inverse of the serum creatinine concentration in

useful only in patients with more advanced diabetic nephropathy (GFR <70 ml/min/1.73 m^2). This implies that a substantial reduction in GFR remains undetected if this method is used in patients with GFR within normal limits. However, it is well documented that the inverse of the serum creatinine concentration declines linearly with time in most patients with chronic renal insufficiency (serum >200 µmol/l) caused by various diseases including diabetes mellitus (7,4).

All ideal endogenous marker of GFR should have a constant rate of syntese, pass freely across the glomerular membran without return to the circulation, and with no alternative route of excretion or catabolism. Thus the serum concentration of such a substance should increase twofold when GFR is reduced by 50%. Our study revealed an increase in serum β_2-microglobulin of 1.87 compared to an increase in serum creatinine of only 1.49. Previous studies have demonstrated that β_2-microglobulin fulfils most of the above mentioned criteria (14,12,13). Recent crossectional studies have suggested that serum concentration of β_2-microglobulin can be used as a reliable and sensitive method in screening for early impaired GFR in IDDM patients with diabetic nephropathy (15,3). Our crossectional study of 17 females and 32 males with GFR values ranging from 148 to 23 ml/min/1.73 m^2 does not supports this suggestion. Normal serum concentrations of β_2-microglobulin were found in 9 out of 31 patients with GFR below 80 ml/min/1.73 m^2 (lower limit of normal range). This discrepancy may be explained by the limited number of patients (3 females and 10 males) studied by Viberti et al. (15), and the lack of GFR determination in the study of Goebel et al. (3). However, it should be mentioned that all patients with GFR below 60 ml/min/1.73 m^2 had elevated serum β_2-microglobulin concentrations while serum creatinine was still normal in 4 out of these 17 patients.

Renal failure due to diabetic nephropathy is the major cause of death (30%) in IDDM patients (5,1). Recent studies (15,8,10), using sensitive and reliable methods for GFR measurements, e.g. ^{51}Cr-EDTA and inulin clearance, have demonstrated that the rate of decline in GFR is constant in the individual patient, but varies considerably between patients, as also demonstrated in our study (0.51 to 1.54 ml/min/month). To obtain information on the prognosis and the effect of treatment, e.g. antihypertensive, in the individual patient, serial determinations of GFR are required. Unfortunately, these methods are time consuming, expensive and often require use of radioactive tracers. Our longitudinal study suggests that serial determination of serum β_2-microglobulin can be used as a simple and fairly reliable method for monitoring GFR in individual patients.

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