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Originals

Glycaemia, arterial pressure and micro-albuminuria in Type 1 (insulin-dependent) diabetes mellitus

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Summary. Plasma glucose control and arterial pressure were assessed in 28 Type 1 (insulin-dependent) diabetic patients with different degrees of micro-albuminuria. They were divided into two groups according to their urinary albumin excretion rate: a low micro-albuminuria group ($n = 16$) with albumin excretion ranging between 12.1 and 28.9 μg/min and a high micro-albuminuria group ($n = 12$) with albumin excretion between 32.4 and 91.3 μg/min. The groups were matched for age, sex and duration of diabetes with the same number of normo-albuminuric (2.0–10.4 μg/min) diabetic control subjects. Both the low and high micro-albuminuria groups had significantly higher glycosylated haemoglobin levels and mean plasma glucose concentrations during a 24-h profile than their respective normo-albuminuric control subjects. A correlation between glycosylated haemoglobin level and urinary albumin excretion rate was found in the whole study group ($r = 0.48$; $p < 0.001$). Arterial pressure (both systolic and diastolic) was significantly higher in the high micro-albuminuria group than in either the control group or the low micro-albuminuria group. A significant correlation was found between arterial pressure and albumin excretion rate in the whole study population ($r = 0.49$; $p < 0.001$) as well as in the pooled micro-albuminuria groups ($r = 0.43$; $p < 0.05$). Multiple regression analysis showed that glycosylated haemoglobin and arterial pressure levels were independently correlated with albumin excretion rates. Diabetic patients with micro-albuminuria of any degree have worse glycaemic control than normo-albuminuric patients. Higher levels of arterial pressure, though often sub-hypertensive, are associated with levels of micro-albuminuria predictive of later development of clinical proteinuria. Thus high plasma glucose and high arterial pressure, or both, characterise those diabetic patients at increased risk of nephropathy. These indices of risk are potentially reversible.

Key words: Plasma glucose, urinary albumin excretion, glycosylated haemoglobin, blood pressure, hypertension, Type 1 diabetes

Prospective studies [1, 2] have shown that certain rates of urinary albumin excretion above the normal range, but falling short of clinical proteinuria (i.e. micro-albuminuria in excess of 30 μg/min), in Type 1 (insulin-dependent) diabetic patients are highly predictive of later development of Albustix-positive proteinuria, itself a regular harbinger of renal failure. The factors responsible for this degree of micro-albuminuria are, however, still unclear and the studies reported so far were not specifically designed to investigate them [1, 2]. A better knowledge of the associations of micro-albuminuria is important, for appropriate therapy might reduce the risk of ultimate renal failure.

In the present study, we relate varying degrees of urinary albumin hyperexcretion in a selected group of Type 1 diabetic patients to prevailing plasma glucose and arterial pressure levels and compare them with a matched group of diabetic control subjects with normal urinary albumin excretion rate.

Subjects and methods

Subjects

During a screening programme of patients attending the diabetic clinic at Guy's Hospital, the 24-h urinary albumin excretion rate was measured. All patients were deemed clinically to be insulin-dependent and had a typical onset of diabetes mellitus at least 2 years previously, negative Albustix (Ames) tests for urinary protein, serum creatinine within the normal range (30–110 μmol/l), were without signs of cardiac failure and had no history of renal or urinary tract disease. All patients were within 10% of ideal body weight and gave informed consent to the study which was approved by the Hospital Ethical Committee.

Twenty-eight patients with micro-albuminuria (the upper limit of the normal range calculated as mean + 2 SD in our laboratory is 12 μg/min) [3, 4] were identified. They were subsequently divided into two groups: 16 with urinary albumin excretion < 30 μg/min (range: 12.1–28.9 μg/min), a level poorly predictive of later clinical proteinuria, and 12 with albumin excretion > 30 μg/min (range: 32.4–91.3 μg/min), a level highly predictive of later Albustix-positive proteinuria [1]. These two groups, termed 'low' and 'high' micro-albuminuria respectively, were matched for age, duration of diabetes and sex (in

Table 1. Clinical features of micro-albuminuric patients and their normo-albuminuric control subjects

	Diabetic patients with		Diabetic patients with	
	Low micro-albuminuria (12–30 μg/min) ($n=16$)	Normo-albuminuria Control subjects ($n=16$)	High micro-albuminuria (>30 μg/min) ($n=12$)	Normo-albuminuria Control subjects ($n=12$)
Sex (M:F)	12:4	12:4	11:1	10:2
Age (years)	31.3 (12 - 53)	32.2 (19 - 54)	34.4 (16 - 58)	33.7 (18 - 59)
Age at onset (years)	18.6 (6 - 38)	20.4 (7 - 39)	18.4 (9 - 32)	17.8 (5 - 34)
Duration of diabetes (years)	11.9 (2 - 27)	11.7 (2 - 26)	16.0 (3 - 34)	15.3 (2 - 36)
Albumin excretion rate (μg/min)	18.1 (12.1- 28.9)	5.4 (2.0- 10.4)	52.0 (32.4- 91.3)	4.1 (2.1- 10.3)
Glomerular filtration rate ($ml \cdot min.^{-1} \cdot 1.73\,m^{-2}$)	120 (90 -161)	124 (83 -136)	111 (61 -182)	122 (99 -140)
Retinopathy	3 background 3 proliferative	5 background no proliferative	4 background 3 proliferative	3 background no proliferative

Results are expressed as mean with the range in parentheses.
No significant differences between either diabetic group and its control group were found in age, sex, duration of diabetes or glomerular filtration rate

Table 2. HbA_{1c} levels in micro-albuminuric diabetic patients and matched normo-albuminuric diabetic control subjects

	Low micro-albuminuria group ($n=16$)	Control group ($n=16$)	p	High micro-albuminuria group ($n=12$)	Control group ($n=12$)	p
HbA_{1c} (%)	12.1± 2.1 (8.3–16.9)	10.5± 1.8 (7.4–13.2)	<0.05	12.2± 1.4 (10.3–14.1)	9.8± 1.2 (7.6–11.4)	<0.001

Results are expressed as mean ± SD with range in parentheses

order of importance) with the same number of insulin-dependent diabetic patients whose albumin excretion rate during the screening procedure had been in the normal range (between 2 and 10.4 μg/min) and who also had normal serum creatinine concentrations and no history of renal dysfunction. We aimed for matching for age within 5 years and duration of diabetes within 3 years. However, in one case this was not possible (Table 1).

Glomerular filtration rate (GFR) was measured in nine of the high micro-albuminuria group and in 12 of the low micro-albuminuria group, and their respective controls (Table 1). Table 1 gives the clinical features of the low and high micro-albuminuria patients and their respective control groups. All patients had negative urine cultures.

Methods

During the 24-h stay in a metabolic ward for screening, a plasma glucose profile was constructed and 24-h urine output collected. No attempt was made to alter diabetic control in these patients who were thus studied under conditions of 'ordinary' glycaemic control.Blood pressure was measured four times (twice supine and twice standing) by a trained observer in the right arm with a conventional mercury sphygmomanometer during the stay in the metabolic ward; Korotkoff phase IV was taken as the diastolic pressure. The mean of all four measurements was used for calculations. Samples for glycosylated haemoglobin (HbA_{Ic}) were taken in the fasting state and measured by electrofocussing [5]. Plasma glucose was measured by the glucose oxidase method (Analox GM6, Analox Instruments, London, UK) and urinary concentration of albumin [6] and β_2-microglobulin by radioimmunoassay (Phadebas-β2-microtest, Pharmacia, Uppsala, Sweden). The inter-assay coefficient of variation for the albumin method is 13.6% and the intra-assay variation is 5.1%. GFR was measured as ^{51}Cr EDTA clearance [7]. Excretion rates were calculated from concentration and 24-h urine volume. Retinopathy was assessed by direct ophthalmoscopy after pupillary dilation. Measurements of blood pressure, plasma glucose, HbA_{1c} and GFR were made in ignorance of the albumin excretion rate of the patients.

Statistical analysis

Statistical evaluation was performed using Student's t-test for unpaired samples as well as linear and multiple regression analysis. Albumin excretion rates were transformed to $\log_{10}$ values for calculations because of their positively skewed distribution.

Results

Both the low and high micro-albuminuria groups had significantly higher levels of HbA_{1c} than their respective diabetic control groups (Table 2). No significant difference was found between the low and high micro-albuminuria groups. There was a significant correlation between albumin excretion rate and HbA_{1c} levels in all diabetic patients combined ($r=0.48$, $p<0.001$), confirming previous findings [3]. That glycaemic control was poorer in the micro-albuminuria patients was also indicated by their 24-h glycaemic profiles (Fig. 1). Mean plasma glucose was consistently higher throughout the day in the micro-albuminuric patients, the difference reaching statistical significance at 16.00, 18.00 and 24.00 h ($p<0.05$). Plasma glucose profiles in the low and high micro-albuminuria groups were similar and statistically indistinguishable. There was no significant

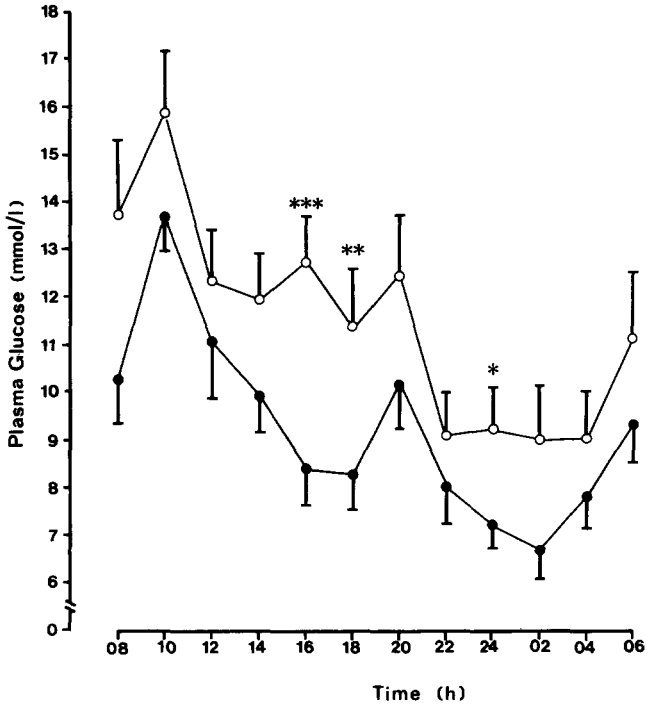

Fig. 1. Mean ± SEM plasma glucose levels in 28 micro-albuminuric diabetic patients (O——O) and 28 normo-albuminuric diabetic control subjects (●——●) during a 24-h profile. * $p < 0.05$ ** $p < 0.02$ *** $p < 0.001$

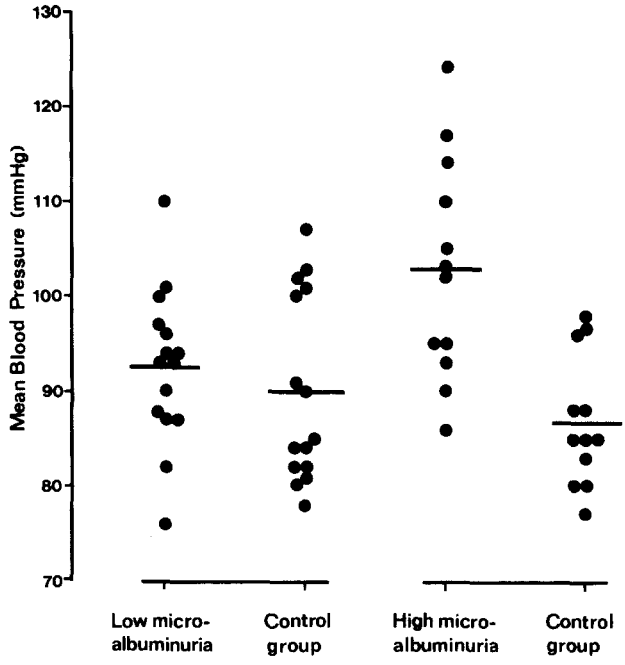

Fig. 2. Mean blood pressures in 16 Type 1 diabetic patients with low micro-albuminuria (albumin excretion rate between 12 and 30 μg/min) and 12 with high micro-albuminuria (albumin excretion rate > 30 μg/min) and their respective normo-albuminuric control groups. Horizontal bars indicate mean values for each group. Mean blood pressure was significantly higher in the group with high micro-albuminuria (102.8 ± 11.7 mmHg) than in the control group (86.8 ± 6.9 mmHg; $p < 0.001$) and the group with low micro-albuminuria (92.5 ± 8.2 mmHg; $p < 0.02$). Mean blood pressure did not differ significantly between the low micro-albuminuria group and its control group (90.0 ± 9.9 mmHg)

linear or non-linear correlation between plasma glucose and albumin excretion rate.

The mean values for systolic and diastolic blood pressures in the low micro-albuminuria group did not differ from those of their control group, but corresponding mean pressure values in the high micro-albuminuria group were significantly higher than those of their control group and of the low micro-albuminuria group (Table 3). The mean blood pressure (calculated as diastolic blood pressure + one-third of pulse pressure) was also significantly higher in the group with high micro-albuminuria (Fig. 2). A significant correlation was found between mean blood pressure values and albumin excretion rates in the whole study population ($r = 0.49$; $p < 0.001$) as well as in the pooled micro-albuminuria groups alone ($r = 0.43$; $p < 0.05$). Multiple regression analysis on the whole study population showed that mean blood pressure and HbA_{1c} related independently to albumin excretion rates (t value = 3.12, $p < 0.005$ and t value = 2.86, $p < 0.01$ respectively, when both variables are included in the regression model), as suggested by lack of significant correlation of their cross product term with albumin excretion (t value = −1.30; NS). All patients had normal urinary excretion rates of β_2-microglobulin. Mean GFR did not differ significantly between the groups (Table 1). No significant correlation was found between HbA_{1c} and mean blood pressure levels nor between albumin excretion rate and age of onset, duration of diabetes or GFR.

Table 3. Systolic and diastolic blood pressures in diabetic patients with micro-albuminuria and matched normo-albuminuric diabetic control subjects

Blood pressure (mmHg)	Low micro-albuminuria group ($n = 16$)	Control group ($n = 16$)	p	High micro-albuminuria group ($n = 12$)	Control group ($n = 12$)	p
Systolic	119.0 ± 9.8 (104 − 135)	117.1 ± 9.5 (103 − 130)	NS	135.5 ± 18.1 (114 − 172)	117.9 ± 7.8 (109 − 132)	< 0.005
Diastolic	78.9 ± 8.5 (61 − 97)	76.4 ± 10.7 (66 − 96)	NS	86.5 ± 8.9 (72 − 100)	71.8 ± 7.2 (62 − 86)	< 0.001

Results are expressed as mean ± SD with range in parentheses.
The high micro-albuminuria group had significantly higher systolic ($p < 0.01$) and diastolic ($p < 0.05$) blood pressures than the low micro-albuminuria group

Discussion

Several previous reports have suggested a relationship between glycaemia and urinary albumin excretion both in man and animals [8–14]. Our findings demonstrate that on a sample day (plasma glucose profile) and over the preceding few weeks (HbA_{1c}) diabetic patients with micro-albuminuria have worse glycaemic control than those with normal albumin excretion rates. Although from a cross-sectional observation it is not possible to exclude the possibility that micro-albuminuric diabetic patients are independently susceptible to more severe diabetes and microvascular disease, there is growing experimental and epidemiological evidence causally relating microangiopathy to glycaemic control [15, 16].

The correlation between HbA_{1c} and albumin excretion rate suggests that chronic hyperglycaemia, with consequent glycosylation of plasma proteins [17] and of structural proteins in the glomerular membrane [18], may play a role in the increased transglomerular flux of albumin, in addition to an acute effect of plasma glucose levels upon glomerular haemodynamics [13, 19].

However, in our study there was no significant difference in glycaemic control between high and low risk micro-albuminuric groups, which suggests that factors other than poor glycaemic control are required in some diabetic patients to advance them into the 'high risk' micro-albuminuric group. There was a difference in average blood pressure between high and low risk groups which could be interpreted in two ways. Albumin excretion $>30\,\mu g/min$ might indicate renal dysfunction sufficient to raise the blood pressure. Alternatively, a raised blood pressure, albeit of modest degree and still within the 'normal' range, may increase albuminuria. These hypotheses are not mutually exclusive. An association between blood pressure and albumin excretion rate has been previously reported in both diabetic and non-diabetic subjects [8, 20, 21] and experimental studies have demonstrated a synergy between high blood pressure and hyperglycaemia upon renal disease [22, 23].

In this and previous studies [1, 2], the average duration of diabetes was longer, though not significantly so, in patients with micro-albuminuria in excess of $30\,\mu g/min$ than in those with lesser degrees of albumin excretion, suggesting that the former patients may have been further along the road to nephropathy. The selection procedure of our study may have obscured the effect of duration by excluding diabetic patients with Albustix-positive proteinuria. However the close matching between the high micro-albuminuria group and the normo-albuminuric control group excludes the possibility that, in this particular group of patients, duration of diabetes is a primary determinant of high micro-albuminuria. The apparent discrepancy with previous studies [1, 2] that reported no difference in the arterial pressure between patients with urinary albumin excretion above or below $30\,\mu g/min$ can probably be ascribed to study design. In previous investigations the blood pressure was measured by different observers in the out-patient clinic, in a non-standard manner. By contrast the present study was specifically designed to investigate this variable with multiple measurements of blood pressure by a single observer. Reduction of blood pressure in essential hypertension and plasma glucose levels in diabetes diminishes albumin excretion [9, 25]. As the relationship between arterial pressure and risk of vascular disease observed in population studies is a continuum [26], the question arises of what levels of arterial pressure merit treatment in diabetes. It may be that in high-risk diabetic patients, i.e. with micro-albuminuria $>30\,\mu g/min$, hypotensive therapy would be beneficial at only moderately elevated levels of blood pressure. Further studies are planned to investigate this hypothesis.

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