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Urinary albumin excretion rate (AER) in newly-diagnosed type 2 Indian diabetic patients is associated with central obesity and hyperglycaemia

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Summary

Urinary albumin excretion rate (AER) was measured in non-diabetic controls ($n = 143$) and newly diagnosed impaired glucose tolerant (IGT, $n = 64$) and non-insulin-dependent (type 2) diabetic patients ($n = 146$). AER progressively increased from non-diabetic [3.7 (1.1–51.3) μg/min, median (5–95th centile)] to IGT [4.8 (1.3–53.7)] and diabetic [7.3 (1.4–91.6)] groups. Eight percent of non-diabetic, 19% of IGT and 23% of type 2 diabetic patients showed 'microalbuminuria' (AER, 20–200 μg/min) (non-diabetic vs diabetic $P < 0.01$, non-diabetic vs IGT NS, IGT vs diabetic NS). AER was directly related to waist-hip ratio ($P < 0.001$) and HbA_1 ($P < 0.01$) in diabetic patients; 80% of diabetic patients with microalbuminuria were men ($P < 0.06$ compared to 'normoalbuminuric' diabetic patients). Association of AER with waist–hip ratio was present in men as well as women. Thus, in the newly diagnosed type 2 Indian diabetic patients AER is associated with central obesity in addition to its well known association with hyperglycaemia. Our findings offer a possible explanation for the increased risk of proteinuria in diabetic men than in women because men are centrally more obese. It could also explain previous reports of higher AER in migrant Asian diabetic patients in the U.K. compared to native white Caucasian diabetic patients because Asians are known to be more centrally obese.

Key words: Urinary albumin excretion rate (AER); Microalbuminuria; Indian (Asian) diabetic patient; Central obesity; Hyperglycaemia

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Introduction

Elevated urinary albumin excretion rate (AER, 'microalbuminuria') is an early manifestation of diabetic nephropathy [1–3] and also predicts macrovascular mortality in type 2 (non-insulin-dependent) diabetic patients [3–5]. Indeed, if vascular damage leading to increased permeability to albumin has occurred in the kidneys, a similar process is usually present elsewhere in the body [6]. Migrant Asian diabetic patients in the U.K. show a higher prevalence of microalbuminuria [7] and clinical proteinuria [8] than native white Caucasian diabetic patients, but little data is available on urinary AER in native Asian subjects, who differ considerably from migrant Asians in many respects (dietary habits, prevalence of obesity, etc.). Diabetes in native Asians is attracting more and more attention due to peculiarities of its clinical features and pathogenetic mechanisms [9,10]. We have reported an association of hyperglycaemia with central rather than generalised obesity in our subjects [11]. In this paper we describe an association between central obesity and AER in our newly diagnosed type 2 diabetic patients.

Subjects and Methods

Details of subjects in the Wellcome Diabetes Study have been described previously [11]. In short, newly diagnosed untreated hyperglycaemic patients were enrolled from outpatient clinics and wards of King Edward Memorial Hospital, Pune, over a period of approximately 2 years. Subjects above 65 years of age, those with a history of myocardial infarction or a stroke within the last 6 months, and those acutely ill or with a severe systemic illness were excluded. Non-diabetic control subjects had attended the outpatient clinics for minor illnesses or were spouses of study subjects. Subjects were classified by WHO criteria (1985) for 75 g (anhydrous) oral glucose tolerance test into normal (2 h plasma glucose < 7.8 mmol/l), IGT (2 h plasma glucose 7.8 to 11.1 mmol/l) and diabetic (2 h plasma glucose $\leqslant 11.1$ mmol/l). Basic clinical characteristics of these subjects are shown in Table 1.

Subjects were carefully instructed about urine collection at a pre-test interview. Those with balanitis/vulvovaginitis, those with symptoms of urinary tract infection or those in whom midstream urine showed leucocytes > 5/HPF as well

TABLE 1

Characteristics of subjects studied

	Non-diabetic ($n = 143$)	Impaired glucose tolerant ($n = 64$)	Type 2 diabetic ($n = 146$)
Age (years)	39 (23–59)	47 (29–63)[a]	45 (30–60)[a]
Men,women	88,55	37,27	92,54
BMI (kg/m^2)	23.6 (17.1–29.7)	26.0 (19.0–33.0)[a]	24.2 (19.4–32.9)[a,b]
W–H ratio	0.84 (0.71–0.97)	0.88 (0.75–0.98)[a]	0.89 (0.74–1.04)[a]
Systolic blood pressure (mmHg)	120 (100–150)	126 (106–160)[a]	130 (104–163)[a]
Diastolic blood pressure (mmHg)	78 (60–96)	80 (64–100)	84 (66–102)[a]
Fasting plasma glucose (mmol/l)	4.6 (3.8–5.6)	5.1 (4.1–6.2)[a]	9.0 (5.2–15.6)[a,b]
HbA_1 (%)	6.1 (5.1–7.1)	6.8 (5.4–9.1)[a]	8.9 (6.5–14.0)[a,b]
AER (μg/min)	3.7 (1.1–51.3)	4.8 (1.3–53.7)	7.3 (1.4–91.6)[a,b]

Median (5–95th percentile); AER = albumin excretion rate; W–H ratio = waist–hip ratio.

[a] $P < 0.05$ vs non-diabetic subjects.

[b] $P < 0.05$ vs IGT subjects.

as those with a history of urinary tract surgery were excluded (six non-diabetic, four IGT, 15 diabetic). Overnight timed (22.00 to 06.00 h) urine samples were collected on the night preceding the oral glucose tolerance test. Urine volume was recorded and an aliquot frozen at −20 °C for albumin assay.

Anthropometric measurements included height, weight, minimum waist and maximum hip circumference. These and supine blood pressure (diastolic phase V) were recorded on the morning of the glucose tolerance test. Plasma glucose (glucose oxidase) and creatinine were measured on an Abbott VP-Super autoanalyser (Irving, Texas, U.S.A.) using standard kits. HbA_1 was measured by a colourimetric method [12]. A trained dietician evaluated the dietary intake of calories, carbohydrates, fats and proteins by the 24 h recall method.

Urine albumin was measured by radial immunodiffusion using rabbit anti-human-albumin antibody (ICN ImmunoBiologicals, Lisle, Illinois, U.S.A.). The sensitivity of the assay is 2.0 mg/l and the coefficient of variation for intra-batch and inter-batch measurements was $<8\%$.

Statistical differences between the groups were tested by Mann–Whitney U or Chi-square test as appropriate and the significance of correlations by Spearman's correlation coefficient (r_s). Multivariate analysis was by multiple linear regression analysis on data normalised by logarithmic transformation whenever necessary.

Results

Type 2 diabetic and IGT patients were older ($P<0.001$, both) and more obese ($P<0.001$, both) than non-diabetic controls; IGT subjects were more obese than diabetic patients ($P<0.05$) (Table 1). Waist–hip ratio, a measure of central obesity, was higher in diabetic and IGT patients compared to non-diabetic subjects ($P<0.001$, both), but there was no significant difference between the IGT and diabetic patients. Fasting plasma glucose and HbA_1 showed the expected differences between the groups. Systolic blood pressure was higher in both diabetic ($P<0.001$) and IGT patients ($P<0.01$) compared to control subjects, but was not significantly different in the two hyperglycaemic groups. Diastolic blood pressure was higher in diabetic patients compared to the other two groups ($P<0.001$, both). All subjects showed normal plasma creatinine concentration.

Microalbuminuria was defined as an AER of 20–200 μg/min as recommended [13]; AER < 20 μg/min was taken as normal. One hundred and thirty-one (92%) non-diabetic controls showed normal AER and 12 (8%) showed microalbuminuria (Fig. 1). One hundred and eleven (76%) diabetic patients showed normal AER and 33 (23%) showed microalbuminuria ($P<0.01$, compared to controls). For the IGT group these figures were 81 and 19% respectively (NS compared to the other two groups). None of the control or IGT subjects showed AER > 200 μg/min; two diabetic patients showed such an elevated AER ('macroalbuminuria'). As a group, type 2 diabetic patients showed higher AER than non-diabetic controls as well as IGT (Table 1).

Diabetic patients with microalbuminuria showed higher HbA_1 ($P<0.01$) and waist–hip ratio ($P<0.05$) compared to those in patients with normal AER (Table 2). There was no significant difference in age, BMI (kg/m^2), fasting plasma glucose, plasma creatinine, systolic and diastolic blood pressure, duration of symptoms before diagnosis, and dietary intake of calories, carbohydrates, proteins and fats between the two groups. Eighty percent of diabetic patients with microalbuminuria were men ($P<0.06$ compared to 'normoalbuminuric' patients). There was no difference in any of the measured parameters between those with normal AER and those with microalbuminuria in non-diabetic control and IGT groups.

On univariate analysis, in non-diabetic and IGT subjects AER was not significantly related to any of the measures studied; in diabetic patients AER was directly related to fasting plasma glucose, HbA_1 and waist–hip ratio ($r_s = \sim 0.3$, $P<0.01$, all). Multivariate analysis of AER (log)

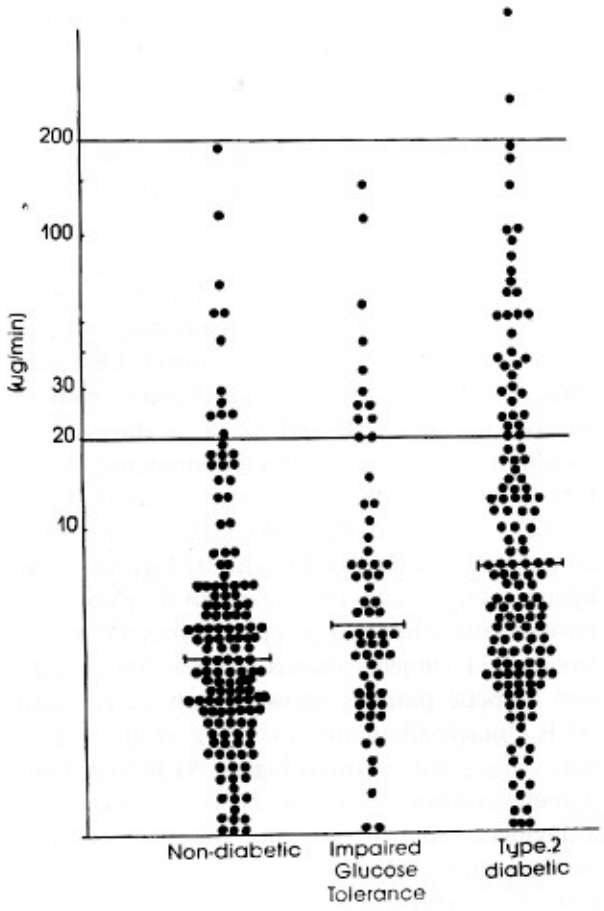

Fig. 1. Distribution of urinary albumin excretion rate (AER) in non-diabetic, IGT and type 2 diabetic patients (log scale). Median value for each group and limits of 'microalbuminuria' are shown.

revealed that, in non-diabetic and IGT subjects, there were no significant associations; in diabetic patients waist–hip ratio ($P<0.001$) and HbA_1 ($P<0.01$) were significantly related (but not age, sex, BMI, fasting plasma glucose or mean blood pressure). For diabetic men, HbA_1 ($P<0.05$) and waist–hip ratio ($P<0.05$), and for diabetic women, waist–hip ratio ($P<0.05$), were significant associations on multivariate analysis.

Discussion

We measured urinary AER in newly diagnosed diabetic patients as part of a prospective study. Twenty-three percent of newly diagnosed, untreated type 2 diabetic patients showed 'at risk' microalbuminuria. Predictive significance of elevated AER for future development of nephropathy in newly diagnosed type 1 diabetic patients is doubtful because of the strong association of AER with severe uncontrolled hyperglycaemia before diagnosis [14], and subsequent 'improvement' in AER after glycaemic control [15]. There is little information on factors affecting AER in type 2 diabetic patients at diagnosis, however the association of microalbuminuria with macrovascular disease in these patients raises the possibility that different pathogenetic mechanisms than those in type 1 diabetic patients might be involved. Similarly, the long duration of asymptomatic hyperglycaemia in type 2 diabetes means that the elevated AER at diagnosis in these patients could be prognostically more significant than in type 1 diabetic patients. The importance of elevated AER in non-diabetic and IGT subjects is not entirely clear, but it is associated with macrovascular disease in non-diabetic white Caucasians [16]. We did not find any significant associations of the measured parameters with AER in our non-diabetic and IGT subjects, but we have not analysed the association of AER with macrovascular disease in this paper. Our prospective observations will help answer some of these questions in our subjects.

We found that the previously described association of AER with hyperglycaemia in type 1 diabetic patients also holds true for our newly diagnosed type 2 hyperglycaemic patients. Thus, AER progressively increased from non-diabetic to diabetic through the IGT group and was directly related to the glycaemic parameters (fasting plasma glucose and HbA_1) in diabetic patients. Men showed higher AER than women and 80% of diabetic patients with elevated AER were men, confirming previous reports of increased risk of nephropathy in diabetic men [17]. Our new finding is the association of AER with waist–hip ratio (in the absence of any relationship with BMI). This association was present for the whole population of diabetic patients as well as for men and

TABLE 2

Features of type 2 diabetic patients with or without microalbuminuria

	AER < 20 μg/min (n = 111)	AER 20–200 μg/min (n = 33)
Age (years)	45 (31–60)	45 (28–60)
Men,women	66,45	26,7
BMI (kg/m^2)	24.6 (19.3–33.9)	24.0 (19.4–32.1)
W–H ratio	0.88 (0.74–1.00)	0.90 (0.77–1.04)[a]
Systolic blood pressure (mmHg)	130 (104–160)	132 (101–173)
Diastolic blood pressure (mmHg)	84 (66–102)	84 (64–119)
Fasting plasma glucose (mmol/l)	9.1 (5.1–15.0)	10.5 (5.2–19.1)
HbA_1 (%)	8.5 (6.5–12.0)	10.1 (6.1–14.8)[a]
Plasma creatinine (μmol/l)	65 (18–124)	77 (18–130)
Dietary intake		
Calories (kcal)	1840 (1360–2496)	1882 (1218–2767)
Protein (g)	51 (35–76)	51 (32–79)
Diabetic symptoms (months)	4 (2–36)	3 (2–72)

Median (5–95th percentile).

[a] $P < 0.05$ between two groups.

women separately. It suggests that central obesity (possibly through its associated metabolic-endocrine factors, i.e. insulin resistance, hyperandrogenism, etc. [18]) could be important in the pathogenesis of microalbuminuria in type 2 diabetes. We have previously reported a direct relationship of waist–hip ratio with fasting and 2 h plasma glucose during oral glucose tolerance test in our subjects [11]. It appears that, in native Indians, central obesity is associated not only with hyperglycaemia (type 2 diabetes) but also with a tendency to 'diabetic' tissue damage early in the course of clinical disease (nephropathy in this case). Central obesity has been shown to be a risk factor for diabetes, dyslipidemia [19] and macrovascular disease in white Caucasians [20,21] as well as in migrant Asians [22], but there is no information on its association with renal problems. Our observation that microalbuminuria is also associated with central obesity adds to the growing list of risks associated with central fat distribution. It would explain the higher risk of diabetic nephropathy in men than in women because men are centrally more obese than women. Higher prevalence of proteinuria in migrant Asian diabetic patients compared to white Caucasians [7,8] could also be related to the more pronounced central obesity of Asians [22]. Subclinical macrovascular disease might underlie this association.

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