Microalbuminuria - a Nephropathy Risk in Non-insulin-dependent Diabetic Asian Community in the U.K.

Jaffar Allawi*

INTRODUCTION

Non-insulin-dependent diabetes diagnosed relatively early in middle age is strikingly common in the 'Asian' Indian community in Britain. In the Southall Diabetes Survey the prevalence of known diabetes in Indian subjects aged 40 to 64 years was five to seven times greater than in comparable Europoids [1]. The early appearance and high prevalence of diabetes in this community raise important questions about the morbid consequences. There are few data on the susceptibility of Indian diabetics to diabetic complications, though in a preliminary clinic study in the Southall area they were found to have the same crude prevalence of retinopathy and symptomatic ischaemic heart disease as European patients despite their younger mean age and shorter mean known duration of diabetes [2, 3].

Several recent studies have monitored 'Microalbuminuria' (Urinary albumin excretion rates exceeding the normal but falling short of that indicated by semi-quantitative tests, such as Albustix), and revealed its important predictive value in the future development of diabetic clinication proteinuria ('Macroproteinuria'; positive urine Albustix test), and/or cardiovascular death [4,5,6,7,8].

In both insulin-dependent as well as non-insulin-dependent diabetics, once macroproteinuria develops, a relentless deterioration in renal functions is inevitable, leading eventually to end-stage renal failure, though in non-insulin-dependent diabetes cardiovascular death often interrupts this progression.

If more diabetics reach end stage renal disease it would place a considerable burden on health services, particularly if, as in the United States, nearly all diabetics are accepted for renal replacement therapy.

Improving overall management and strict diabetic control may reduce microalbuminuria [9,10,11]. This would help in preventing or delaying deterioration to renal failure and the need for renal dialysis and kidney transplantation. Also, if microalbuminuria fulfils its potential as an indicator of reversible nephropathy, screening of all diabetics and intensive management of high risk ones could constitute a considerable advantage in the long term management of diabetes.

The present study applies the technique of measurement of albumin excretion to the comparison of complications in Indian non-insulin-dependent diabetics, Indian non diabetic control subjects and Europoid non-insulin-dependent diabetics.

METHODS AND VARIABLES USED IN THIS STUDY

SUBJECTS:

Indian Non-insulin-dependent patients:

All 305 Indian patients aged between 20 and 65 years due to attend the diabetic clinic at Ealing Hospital over 10 months were asked by letter in Punjabi/Gujarati and English languages to participate in the study. Two hundred and thirty seven patients attended and were intitially studied. Of those who did not attend, 15 had moved and could not be traced. The response rate was thus 82% (237/290). Subsequently, 67 patients receiving insulin treatment were excluded. Thirteen patients found to have urinary tract infection on examination of midstream urine specimen and three whose urine sample were lost were excluded. Thus 154 patients were included in the study.

Europoid Non-insulin-dependent patients:

Eighty five Europoid patients, age under 65 years, attending the diabetic clinic at Guy's Hospital who were not receiving insulin were invited to participate in the study over a period of 14 months so that frequent attenders were not selectively recruited. The response rate was 100%. These patients made a timed overnight urine collection and spent the next day in the metabolic ward, when a midstream urine sample was obtained to exclude urinary infection; none was found.

* *From Unit for Metabolic Medicine, Guy's Hospital Campur, London Sel 9 RT-U.K.*

Control Indian subjects:

Control subjects aged 36-55 years were obtained by random selection from a general practice age – sex register from Indian patients in Southall. Those known to have diabetes and one subject who was undergoing treatment for end-stage renal failure were excluded. From a list of 183 subjects invited, 129 agreed to participate in the study, a response rate of 71%.

A proforma was completed for each patient with clinical details including the presence of known hypertension; height and weight, from which the Body Mass Index [weight (kg) over height (m^2)] was calculated.

Blood pressure was measured with a Hawkesley random zero sphygmomanometer after subjects had been seated for 10 minutes. The mean of two readings from the tight stretched arm was recorded; the Korotkoff phase V was used to define the diastolic end point.

Fasting blood was examined for the glucose contents, glycosylated haemoglobin A_{1C} and urea and creatinine content. Urinary albumin concentration (UAC) was estimated in the early morning urine sample and albumin-creatinine ratio (ACR) was calculated in each instance, urinary albumin concentration in mg/mmol divided by urinary creatinine value in mmol/l.

RESULTS: Clinical and biochemical parameters in the three groups (Mean and standard deviation) have been presented in Table I and II.

Indian diabetics were significantly younger and had shorter duration (from date of diagnosis) of diabetes than Europoid diabetics but were significantly older than the Indian controls in both sexes.

Systolic blood pressure did not differ significantly between groups amongst males but in females Indian controls had much lower blood pressure than Indian diabetics. In males diastolic blood pressure in the Indian controls was higher than the Indian diabetics while the reverse is apparent amongst females.

Indian diabetics are similar in height to the controls both in males and females but are significantly shorter than Europoid diabetics. Indian diabetics are significantly lighter than Europoid diabetics and significantly heavier than Indian controls in females but in males.

In males, Indian and Europoid diabetics have similar levels of obesity. Female Europoid diabetics are the most obese group while Indian controls are the least obese.

Fasting blood glucose and HbA_1 did not differ significantly between Indian and Europoid diabetics. Both these variables were significantly lower in Indian controls. These differences were apparent in males and females.

Table I: GROUP COMPARISONS FOR CONTINUOUS VARIABLES MEANS (Standard Deviation). ALL THREE GROUPS – MALES

MALES	EUROPOID DIABETICS	INDIAN DIABETICS	INDIAN CONTROL
AGE (years)	57.25 (7.37)	50.97 (9.78)	44.98 (5.91)
DURATION (years)	7.73 (2.29, 4.63)	2.85 (2.28, 3.54)	
SYSTOLIC B.P. * (mmHg)	137.27 (18.11)	133.24 (18.42)	136.29 (29.69)
DIASTOLIC B.P. * (mmHg)	80.95 (10.10)	83.08 (10.48)	89.96 (19.71)
HEIGHT (cm)	172.15 (7.25)	168.53 (8.41)	170.27 (6.04)
WEIGHT (Kg)	79.04 (16.41)	74.84 (11.64)	72.98 (9.90)
B.M.I. (Kg/m^2)	26.66 (5.16)	26.35 (3.81)	25.14 (2.81)
FBG (mmol/L)	9.33 (8.49, 10.26)	9.69 (9.09, 10.34)	5.53 (5.25, 5.82)
HbA_1(%)	8.80 (1.59)	8.58 (2.64)	6.87 (1.35)
PLASMA UREA (mmol/L)	6.98 (1.79)	5.52 (1.53)	4.62 (1.06)
PLASMA CREATININE (mmol/l)	89.51 (21.46)	108.36 (26.58)	92.73 (12.88)
URINE ALBUMIN CONCENTRATION (microg/ml)	6.77 (5.26, 8.72)	11.69 (9.14, 14.98)	5.44 (4.00, 7.40)
URINE CREATININE (mmol/l)	7.37 (6.35, 8.55)	9.30 (8.29, 10.44)	12.16 (10.59, 13.96)
ACR (microg/mmol)	0.92 (0.72, 1.18)	1.25 (0.99, 1.58)	0.44 (0.33, 0.59)

BMI : Body Mass Index; HBA1 : Glycosylated Haemoglobin A1; FBG : Fasting Blood Glucose.
ACR : Albumin-Creatinine Ratio.
* : Sitting Systolic Blood Pressure.
* : Sitting Diastolic Blood Pressure.

Table 2 : GROUP COMPARISONS FOR CONTINUOUS VARIABLES MEANS (Standard Deviation). ALL THREE GROUPS – FEMALES

MALES	EUROPOID DIABETICS	INDIAN DIABETICS	INDIAN CONTROL
AGE (years)	56.43 (6.83)	49.93 (8.75)	43.19 (5.70)
DURATION (years)	5.00 (3.95, 7.63)	3.69 (3.00, 4.51)	
SYSTOLIC B.P. * (mmHg)	143.20 (16.30)	140.41 (25.26)	122.14 (18.67)
DIASTOLIC B.P. * (mmHg)	84.87 (9.96)	83.00 (11.18)	76.84 (11.98)
HEIGHT (cm)	161.30 (6.43)	153.75 (5.87)	154.93 (6.43)
WEIGHT (Kg)	81.24 (17.71)	68.49 (13.22)	61.99 (9.71)
B.M.I. (Kg/m^2)	31.22 (6.35)	28.95 (5.28)	25.79 (4.07)
FBG (mmol/L)	10.28 (9.12, 11.59)	10.50 (9.65, 11.43)	5.05 (4.88, 5.22)
HbA_1(%)	9.19 (1.88)	9.30 (2.00)	6.83 (1.19)
PLASMA UREA (mmol/L)	6.46 (1.53)	4.87 (2.94)	4.12 (1.14)
PLASMA CREATININE (mmol/l)	75.03 (22.51)	95.77 (35.85)	75.85 (11.86)
URINE ALBUMIN CONCENTRATION (microg/ml)	4.41 (2.68, 7.24)	9.60 (6.39, 14.42)	4.22 (3.55, 5.01)
URINE CREATININE (mmol/l)	5.94 (4.93, 7.16)	5.75 (4.87, 6.78)	7.48 (6.53, 8.57)
ACR (microg/mmol)	0.74 (0.47, 1.16)	1.66 (1.12, 2.46)	0.56 (0.47, 0.66)

BMI: Body Mass Index; HBA_1: Glycosylated Hemoglobin A_1; FBG: Fasting Blood Glucose.
ACR: Albumin Creatinine Ratio.

Plasma urea was significantly higher in Europoid diabetics than in Indian diabetics. The latter group had a higher mean plasma urea than Indian controls though this difference did not reach statistical significance in females.

Plasma creatinine was significantly higher in Indian diabetics than either Europoid diabetics or Indian controls and was apparent in both sexes. UAC differed between the groups in much the same way and was highest in Indian diabetics.

Male Europoid diabetics had a significantly lower mean urinary creatinine than male Indian diabetics. In females the difference between Indian and Europoid diabetics was non-significant and minimised. In both sexes, urinary creatinine was significantly higher in Indian controls than in Indian diabetics.

The Indian diabetics in both sexes had the highest mean ACR. Europoid diabetics had a lower mean value than Indian diabetics in females but not males, which reached statistical significance in females but not males.

Amongst Asians of both sexes the mean value was much lower in controls than diabetics.

The percentage of males with systolic blood pressure above or equal to 160 mmHg was highest amongst Indian controls but differences between groups were not significant. In sharp contrast, very few female Indian controls had a systolic blood pressure above this limit and it was the female Indian diabetics who appeared most at risk. The difference between these two Indian groups was highly significant.

Much the same pattern was found for diastolic blood pressure. In males, Indian controls were again at greatest risk while in females, Indian diabetics had a slightly higher risk than Europoid diabetics with the lowest percentage for controls.

Approximately 15-20% of males in each group were treated for hypertension. In women, 28% of diabetics were treated compared to only 11% of controls. Therefore the lower blood pressures found in female controls was not an artefact due to treatment.

The correlation coefficients measuring the association between ACR and eleven independent variables were calculated (Table 3).

A positive association between blood pressure (both systolic and diastolic) was apparent in the Indian diabetics and their controls for both sexes.

These associations irrespective of sex or diabetes were of a similar order of magnitude. A positive association was also found in Europoid diabetics but this did not reach conventional statistical significance. This may in part have been due to smaller numbers (correlation coefficients are of approximately the same magnitude) for Europoid female patients.

Table 3 : CORRELATIONS WITH Log10 ALBUMIN CREATININE RATION. ALL THREE GROUPS

VARIABLES	INDIAN DIABETICS		EUROPID DIABETICS		INDIAN CONTROLS	
	Male	Female	Male	Female	Male	Female
AGE (years)	-0.04	0.02	-0.05	-0.16	0.08	0.14
Log 10 DURATION (duration in years	-0.07	0.25 (p=052)*	-0.11	0.25		
SYSTOLIC B.P. + (mmHg)	0.29** (p=0.0042)	0.35** (p=0.0052)	0.21	0.26	0.29* (p=0.03)	0.31* (p=0.019)
DIASTOLIC B.P. +(mmHg)	0.30** (p=0.0035)	0.28* (p=0.030)	0.16	0.30	0.30* (p=0.024)	0.37** (p=0.0046)
HEIGHT (cm)	-0.18	0.31* (p=0.015)	-0.03	-0.33 (p=0.074)	0.09	-0.03
WEIGHT (Kg)	0.11	0.13	0.11	0.05	0.13	-0.03
B.M.I. (Kg/m^2)	0.23* (p=0.025)	0.03	0.13	0.18	0.11	0.16
Log 10 FBG (FBG in mmol/L)	0.24* (p=0.018)	0.07	-0.07	0.61*** (p=0.0004)	0.18	0.21
HbA_1 (%)	0.06	0.15	-0.19	0.24	0.18	0.10
PLASMA UREA (mmol/L)	0.17	0.58** (p=0.0001)	0.26 (p=0.062)	-0.18	0.24 (p=0.080)	0.17
PLASMA CREATININE (mmol/l)	0.00	0.54***	-0.03	-0.15	0.07	-0.12

BMI : Body Mass Index. + Sitting Systolic Blood Pressure. * : $p < 0.05$

DISCUSSION

Study has been directed to seek possible racial differences in micro-albuminuria and its predictive value of association with other variables.

The predictive value of albumin-creatinine ratio (ACR) in the morning urine sample compared to urinary albumin concentration UAC has been examined in detail.

Duration of known disease, a well known risk factor for microvascular complications of diabetes did not show any significant difference between the two diabetic populations in this study. Also, known duration did not show any significant correlation with UAC and ACR in univariate and in multivariate analysis.

Gender as a risk factor of nephropathy had been debated. Men and women are probably equally affected by diabetic nephropathy although a number of studies have found slightly greater rates of diabetic nephropathy among insulin-dependent diabetic men [12]. In this study, looking at UAC, ACR and other variables in univariate as well as multivariate analysis to ascertain any significant gender difference was inconclusive. The differences and associations were varied but diabetic women may be at more risk than men due to their higher blood pressure and greater obesity.

Obesity as such may not have direct effect on UAC or ACR but probably contributes through other mechanisms such as poor control, hyper-insulinaemia and high blood pressure. In this study, weight in all the Indian diabetics and body mass index (BMI) in the male Indian diabetics was significantly associated with UAC and ACR. Europoid diabetics and Indian controls did not show the same association. The association disappears when using multivariate analysis.

In this study, when looking at both genders together, hypertension was positively associated with UAC and ACR in the Indian diabetics but not in the Europoids. The association of blood pressure, UAC and ACR in the Europoid women as stated earlier showed higher correlation coefficients than Europoid men but did not reach significance due to their small number. However, in the best multivariate analysis models, blood pressure is only significant in male Indian diabetics and female Indian controls. Previous reports have given conflicting results on this point in Europoids. In the Bedford study significant positive correlations were obtained between systolic blood pressure and the logarithm of albumin excretion rate in newly diagnosed diabetics [13, 14]. A low degree of positive correlation between albumin excretion rate and systolic blood pressure was also noted in subjects with fasting hyperglycaemia, known diabetics, and control subjects aged 60-74 in Denmark [15] but not in Danish patients stratified by duration of diabetes and urinary albumin concentration [5].

In another study, albumin excretion rate was found to be increased before treatment in non diabetic subjects with hypertension and to fall significantly after treatment [16]. Such discrepancies may be real or due to differences in methodology or sample size or to sampling variation. Nevertheless, the higher proportion of patients with increased urinary albumin concentration and ACR's among the Indian diabetics in this study cannot be ascribed to higher average blood pressure. Conceivably, the kidneys of Indians may be more vulnerable to the effects of raised blood pressure of diabetes, or both.

When looking at the biochemical variables and their association with UAC, and ACR, there was a significant difference in the mean of plasma creatinine between Indian diabetics and Europoids (higher in the Indian diabetics). Also, a moderate negative correlation between serum creatinine and ACR was noted but was most significant when using multivariate analysis in both Indian diabetics and Europoids. This may indicate some association between renal impairment and microalbuminuria. However, the findings of high serum creatinine in some patients with low ACR and vice-versa emphasise that serum creatinine is not a very exact measure of kidney function and that ACR may be associated with factors other than renal [6].

Means of fasting blood glucose and HbA1 did not differ significantly between diabetics of either ethnic group or between sexes within ethnic groups. They were expectedly much lower in the reference population. Looking at correlations with ACR, fasting blood glucose was positively associated except for Europoid males. The association appeared to be quite strong in Europoid females. In the Indian groups the only significant correlation was in male Indian diabetics.

On the other hand, in the stepwise multivariate analysis blood glucose level was an important predictor of ACR especially in the females of the two races. This is particularly interesting as HbA_1, a longer term assessment of blood glucose control, showed a low order of univariate correlation. The day-to-day variation in ACR and UAC is well recognised [17] and it is possible that blood glucose is a significant factor in this variation.

SUMMARY:

Ratio of albumin to creatinine concentration has been measured in samples of first urine voided in the morning 154 Indian non-insulin-dependent diabetics, 85 Europoids with non-insulin-dependent diabetes and 129 control group of Indians. Indian NIDDM had a higher percent with microproteinuria than Europoids, (28.6% Vs 17.4%); in Indian controls it was 10.1%.

There was no significant correlation between the albumin – creatinine ratio and age, body mass index, duration of diabetes Hb A_{1c}, hypertension and raised albumin-creatinine ratio were significantly associated. This was much more evident amongst Indians than Europoids.

Indian diabetics carry a higher risk of developing diabetic renal complications.

REFERENCES

1. Freedman BJ. Caucasian. Br Med J 1983; 288: 696.

2. Mather HM, Keen H. The Southall diabetes survey: prevalence of known diabetes in Asians and Europeans. Br Med. J 1985; 291:1081.

3. Nicholl CG, Levy JC, Mohan V, Rao V, Mather HM, Asian diabetes in Britain: Clinical profile. Diabetic Med 1986; 3: 257.

4. Jarrett RJ, Viberti GC, Argyropoulos A, Hill RD, Mahmud U, Murrells TJ. Microalbuminuria predicts mortality in non-insulin-dependent diabetes. Diabetic Med 1984; 1:17.

5. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med 1984; 310: 356.

6. Schmitz A, Vaeth M, Microalbuminuria: A Major Risk Factor in non-insulin-dependent Diabetes. A 10-year Follow-up Study of 503 patients. Diabetic Med. 1988; 5: 126.

7. Parving HH, Oxenboll B, Svendsen PAa, Sandahl Christiansen J, Andersen AR. Early detection of patients at risk of developing diabetic nephropathy. A longitudinal study of urinary albumin excretion. Acta Endocr 1982; 100: 550.

8. Viberti GC, Hill RD, Jarrett RJ, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent mellitus. Lancet 1982; 1: 1340.

9. Viberti GC, Pickup JC, Jarrett RJ, Keen H. Effect of control of blood glucose on urinary excretion of albumin and B_2 microglobulin in insulin-dependent diabetes. N Engl J Med. 1979; 300: 638.

10. The Kroc Collaborative Study Group: Blood glucose control and evolution of diabetic retinopathy and albuminuria. N Engl J Med. 1984; 311: 365.

11. Wiseman MJ, Saunders AJ, Keen H, Viberti GC: Effect of blood glucose on glomerular filtration rate and kidney size in insulin-dependent diabetics. N Engl J Med. 1985; 312: 617.

12. Eggers PW, Connerton R, Mc Mullar M. The Medicare experience with end-stage renal disease: Trends in incidence, prevalence and survival. Health care Financing Review 1984; 5, 69.

13. Keen H, Chlouverakin C, Fuller JH, Jarrett RJ. The concommitants of raised blood sugar, Studies in newly detected hyperglycaemia. In urinary albumin excretion, blood pressure and there relation to blood sugar level. Guy's Hosp Rep. 1969; 118-247.

14. Jarrett RJ, McCartney P, Keen H, The Bedford survey: ten year mortality rates in newly diagnosed diabetics, borderline diabetics and normoglycaemic controls and risk indices for coronary heart disease in borderline diabetics. Diabetologia 1982; 22: 79.

15. Damsgaard EM, Mogensen CE. Microalbuminuria in elderly hyperglycaemic patients and controls. Diabetic Med 1986; 3: 430.

16. Pedersen EB, Mogensen CE. Effect of antihypertensive treatment on urinary albumin excretion, glomerular filtration rate, and renal plasma flow in patients with essential hypertension. Scand J Clin Lab Invest 1976; 36: 231.

17. Gating W, Mullee MA, Knight C, Hill RD. Microalbuminuria in Diabetes: Relationships between urinary albumin excretion and Diabetes related variables. Diabetic Med 1988; 5, 348.