Albuminuria And Cardiovascular Complications In Diabetic Patients

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The objective of our study was to determine whether presence of micro- or macroalbuminuria in diabetic patients predicts the presence of coronary heart disease and other risk factors. Eighty patients with history of diabetes of more than 10 years duration were studied. Their urine was tested for albumin with dipstick and radioimmunoassay. Patients were divided into three groups: group-I with macroalbuminuria, group-II with microalbuminuria and group III without albuminuria. The first two groups collectively had higher prevalence of ischaemic heart disease (38.3% vs. 27.3%) and had significantly higher mean value of serum cholesterol (222.3 ± 67.4 vs. 187.6 ± 25.1 p< .001) as compared to group-III (without albuminuria). They also had significantly higher mean serum creatinine and urea level (1.6 ± 1.3 vs. 0.88 ± 0.24 p < .001) and 52.6 ± 29.1 vs. 34.1 ± 8.4 p < .001). In patients with micro- or macroalbuminuria, values for mean blood pressure, triglycerides and low density lipoprotein were higher; and high density lipoprotein were lower than those without albuminuria, but this difference did not reach the level of statistical significance. We conclude that the patients with diabetes of more than 10 years duration frequently have micro- or macro albuminuria. These patients have more chances of having compromised renal functions and co-existent coronary heart disease. The later can be best explained on the basis of higher frequency with which other well known risk factors particularly hypercholesterolemia is seen in this group. Strategy for routine screening of albuminuria in long standing diabetics appears justified to identify people at greater risk. Meticulous metabolic control in such patients may reduce the prevalence of coronary heart disease and end-stage renal failure.
KEY WORDS: Diabetes mellitus, microalbuminuria, macroalbuminuria and coronary heart disease.

Diabetes mellitus is characterized by microvascular complications such as retinopathy, nephropathy and neuropathy.[1] Macrovascular complications like ischaemic heart disease, cerebrovascular accidents and peripheral vascular disease are also commonly seen in diabetic patients.[2] It has been observed that albuminuria may antedate these complications by several years.[3] Later it was realized that elevated albumin excretion even below the proteinuric (dipstick-positive) level might also be important in the pathogenesis of such complications.[4] This concept became clearly established with the availability of sensitive assays, which could detect urinary albumin as low as 20-200 microgram/L. This level was considered abnormal but was below the sensitivity of dipstick method and hence called microalbuminuria. Soon after that some studies demonstrated that these patients are likely to develop overt nephropathy.[5] However all patients with microalbuminuria do not proceed to frank proteinuria and renal failure, but still have increased mortality.[6] In fact the major cause of death in such patients is associated cardiovascular disease and not renal failure. The concept of microalbuminuria as a predictor of increased mortality due to associated cardiovascular disease became further established when the first study documenting the association between microalbuminuria and coronary heart disease, abnormal lipid profile and hypertension was published.[7] Although their exact relationship is not clear, albuminuria does predict poor prognosis, and advocates some intervention of therapy to prevent such an out-come. The objective of our study was to test this hypothesis in our own population by determining:

1. The incidence of micro- and macroalbuminuria in patients with diabetes of more than 10 years duration.
2. The prevalence of coronary heart disease, hypercholesterolaemia, hypertriglyceridaemia and other coronary risk factors in the patients with, and without albuminuria.
3. The kidney functions in both groups.

Patients And Methods:

Patients attending Diabetic Clinic, Mayo Hospital, Lahore with known history of diabetes for more than 10 years were included in the study. This arbitrary cut-off line was made to ensure the inclusion of a reasonable number of patients with albuminuria. A detailed history was taken and previous medical record reviewed. Their height, weight, and blood pressure were recorded. A thorough physical examination, especially directed to pick up diabetic complications was performed. A fasting and 2-hours postprandial blood sugar, blood urea and creatinine, were determined. Serum cholesterol, LDL, HDL and triglycerides were estimated on a 16-hours fasting sample. On subsequent visits their early morning urine was collected and tested for sugar, proteins and creatinine. Those patients who had positive dipstick test for albumin were called group-I. Urine of patients with negative dipstick test was frozen for further testing for microalbuminuria at the Federal Postgraduate Medical Institute using radioimmunoassay technique. Those who had positive test for microalbuminuria were called group-II and others (with both negative dipstick and radioimmunoassay) were placed in group-III. Although timed urinary albumin excretion is considered superior by some authorities,[8] we preferred estimation of albumin on a single early morning specimen. As this study was conducted in the out-patients, correct measurement of timed urine would have been unreliable. ECG was recorded to screen ischaemic heart disease. Where necessary, cardiac enzymes, echocardiography and exercise tolerance test was also performed.

Exclusion criteria: Diabetic patients with additional renal disease e.g. calculi, glomerunephritis or autoimmune disease etc. were excluded. End stage renal failure, pregnancy and secondary diabetes were also excluded.

Results

Summary of our results is presented in Table 1 & 2.

Table 1. Characteristics of study patients.

Parameter	Value
Age (yr)	51.6 10.2
Sex	21 (26.3%) male; 59 (73.8%) female
Duration of diabetes mellitus (yr)	13.7 ± 5.4
Type of diabetes mellitus	13 (16.3) IDDM; 67 (87.8%)NIDDM
Height (cm), weight (kg) & BMI	158.9 ± 9.8, 68.1 ± 11.6 & 27.1 ± 4.7
Waist (cm), hip (cm)& waist hip ratio	98.3 ± 11.2, 97.7 ± 14.6 & 1.00 ± 0.09
Systolic, diastolic & mean BP (mmHg)	111.5 ± 17.7
Smoking	7 (8.8%) smokers 73 (91.3%) non-smoker
Sedentary life style	27 (33.8%)
Blood sugar fasting (mg/dl)	173.4 ± 74.0
Blood sugar post-prandial (mg/dl)	271.4 ± 98.2
Serum cholesterol (mg/dl)	207.9 ± 56.5
Serum triglyceride (mg/dl)	184.26 ± 136.7
Low density lipoprotein (mg/dl)	134.6 ± 53.1
High density lipoprotein (mg/dl)	48.2 ± 13.1
Blood urea (mg/dl)	44.9 ± 24.8
Serum creatinine (mg/dl)	1.31 ± 1.05
Urinary creatinine (mg/dl)	75.15 ± 47.08
Uric acid (mg/dl)	6.7 ± 6.7

Table 2. Comparison of patients with and without albuminuria as regards to presence of IHD and various risk factors.

Parameter	Group-I (n = 33) Normal urine	Group-II (n = 9) Microalbumin uria	Group-III (n=38) Macroalbumin uria	Group II+III(n = 47) Total albuminuria
Age(yr.)	51.4 ± 11.4	53.1 ± 7.9	51.4 ± 9.9	53.2 ± 8.9
Duration (yr.)	13.1 ± 3.6	13.7 ± 5.5	14.2 ± 6.7	13.9 ± 6.1
Ischaemia or infarction	10 (30.3%)	4 (44.4%)	13 (34.2%)	17 (36.1%)
Blood sugar fasting (mg/dl)	165.8 ± 59.9	207.2 ± 97.0	172.1 ± 78.9	172.9 ± 80.3
Blood sugar postprandial	256.7 ± 71.9	285.1 ± 103.4	280.8 ± 116.1	281.7 ± 112.7
Mean blood pressure (mmHg)	1104 ± 16.9	112.4 ± 18.6	117.6 ± 19.9	112.2 ± 18.2
Body mass index (BMI)	27.6 ± 5.0	27.5 ± 5.2	26.5 ± 4.3	26.7 ± 4.4
Total cholesterol (mg/dl)	187.6 ± 25.1	210.7 ± 68.5	225.0 ± 67.7	217.4 ± 67.4
LDL (mg/dl)	117.4 ± 40.4	135.3 ± 72.1	149.3 ± 54.7	136.6 ± 47.4
HDL (mg/dl)	53.5 ± 15.1	48.3 ± 9.7	43.6 ± 10.2	49.4 ± 14.1
Triglycerides (mg/dl)	123.5 ± 41.4	188.7 ± 113.9	235.9 ± 171.9	218.0 ± 236.8
Serum creatinine (mg/dl)	0.88 ± 0.24	1.10 ± 0.5	0.99 ± 0.09	1.3 ± 1.0
Serum urea (mg/dl)	34.1 ± 8.4	40.8 ± 17.3	44.1 ± 19.7	44.0 ± 20.3
Waist hip ratio	0.98 ± 0.1	1.06 ± 0.1	1.0 ± 0.1	1.01 ± 0.1

Key: LDL, Low density lipoproteins; HDL, high density lipoproteins.

Out of 80 patients, 21 (26.3%) were males and 59 (73.7%) females. Their mean age was 51.6 ± 10.2 years. The mean duration of diabetes was 13.7 ± 5.4 years. Values for mean weight, height, and body mass index were 68.1 ± 11.6 kg, 158.9 ± 9.8 cm and 27.1 ± 4.6 kg/m^2 respectively. Female patients had body mass index slightly greater than that of males (28.0 ± 4.4 vs. 24.5 ± 4.3). Approximately sixty three percent were overweight (BMI > 25 kg/m^2). Eighty four percent fulfilled the criteria of NIDDM and the remaining 16% were placed in the IDDM group. Forty seven patients (58.8%) had albuminuria, out of which 9 (11.3% had micro and rest (47.5%) had macroalbuminuria. Our most striking finding was the greater prevalence of ischaemic heart disease in diabetic patients with albuminuria (38.3%), than those without (27.3%) (Fig 1). The mean serum cholesterol level in the former group was also significantly higher than that in the later (222.3 ± 67.4 vs.187.6 ± 25.1 p<.001)(Fig 2). They also had significantly higher mean serum creatinine and urea levels (1.6 ± 1.3 vs.0.88 ± 0.24 p < .001) and 52.6 ± 29.1 vs. 34.1 ± 8.4. p < .001) (Fig.3). In patients with albuminuria (micro- and macro collectively), values for mean blood pressure, triglycerides and low density lipoprotein were higher, whereas high density lipoprotein was lower than that in patients without albuminuria, but the difference did not reach the level of statistical significance.

Figure 1. Chart showing incidence if IHD in patients with normal urine, microalbuminuria, macrialbuminuria & all albuminuric patients.

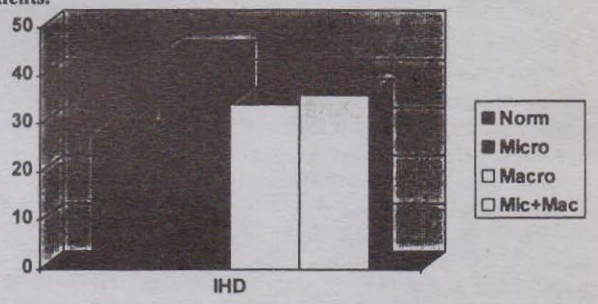
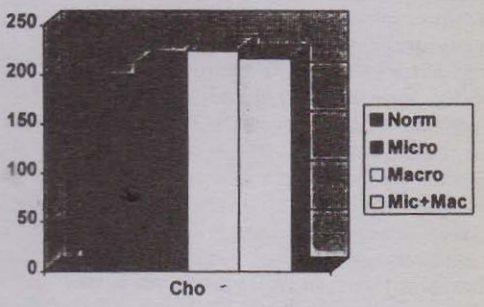


Figure:2. Value of mean serum cholesterol in patients with normal urine, microalbuminuria, macroalbuminuria and all albuminuric patients.

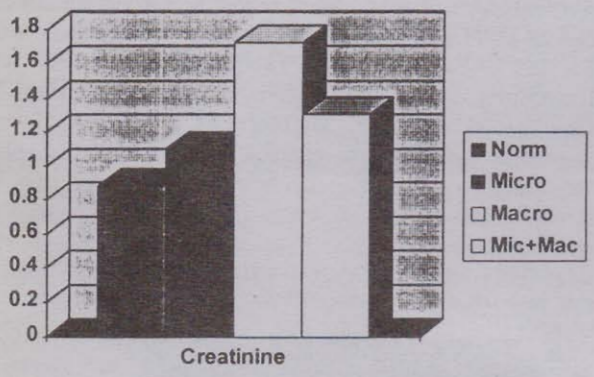


Discussion

Albuminuria is considered to be an important predictor of overt diabetic nephropathy. In our study, reiterating this fact, the presence of much higher mean values of serum creatinine and urea in diabetic patients with both micro and macroalbuminuria suggests that the process of renal failure had already begun at this early stage. Typically these patients develop end-stage renal disease (ESRD) in

5-15 years.[4] Meticulous glycaemic control,[10] protein restriction,[11] phosphate lowering and ACE inhibitors[12] have been demonstrated to slow down the progressive renal damage. Although the patients are asymptomatic at this stage, any preventive intervention has to be instituted early to prevent ESRD.

Figure 3. Value of mean serum creatinine in patients with normal urine, microalbuminuria, macroalbuminuria and all albuminuric patients.



As stated earlier, microalbuminuria has also been postulated to be an indicator of poor prognosis due to increased cardiovascular morbidity and mortality in long-standing diabetes mellitus.[8,9] In our study, a higher percentage of patients with albuminuria had evidence of ischaemic heart disease compared to those whose urine was negative for albumin. This finding is in keeping with that of Messent et al.[13] A possible explanation could be the presence of a significantly higher mean total cholesterol and low-density lipoproteins (LDL) level in these patients. The exact relationship between the albuminuria and these lipid abnormalities (cause and effect?) remains obscure. They could well be two different manifestations of some common underlying abnormality such as poor insulin sensitivity and hyperinsulinaemia.[14] Theoretically, intact insulin sensitivity in the liver (mediated through IGF receptors) and selective insulin resistance in the muscles and adipose tissue (dependent only on insulin receptors), in the face of hyperinsulinaemia could well explain the greater hepatic production of lipoproteins. This could ultimately lead to atherosclerosis and increased cardiovascular mortality.[15]

Another contributory factor responsible for macrovascular disease, may be concomitant hypertension.[16] In our study, the mean values of systolic, diastolic and mean blood pressures in patients with albuminuria were high, although it failed to reach the level of statistical significance. Hypertension in such patients may be the result of compromised renal functions due to diabetic nephropathy, or may be due to direct vasoconstriction or sodium retaining effect of insulin.[17] Since many patients with diabetes actually have hyperinsulinaemia,[18] it appears that insulin may at least partly be responsible for hypertension. It is interesting to note that hypertension itself worsens proteinuria[19] hence producing a vicious cycle ultimately leading to nephropathy, atherosclerosis and coronary heart disease.

The timely detection of proteinuria, possible by routine screening, can detect patients at a greater risk of developing end-stage renal failure and coronary heart disease. Remedial measures such as tight glycaemic control, low protein diet, and control of blood pressure if taken early, could reduce the progression of diabetic nephropathy and possibly also atherosclerosis.[20] A follow-up study involving a larger number of patients recruited at an early stage of diabetes is needed to establish a definite association of progressive renal disease and cardiovascular complication at the early stage of microalbuminuria.

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