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Screening for Microalbuminuria in Newly Detected Diabetes Mellitus Type 2

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Abstract: We studied 120 newly diagnosed diabetes mellitus type 2 patients for detection of microalbuminuria through the dipstick method. Only patients who were diagnosed with diabetes mellitus type 2 at the time of admission were included in the study. Known diabetics were excluded. Early morning midstream urine is taken for sampling. HbA1c in females was higher and more statistically significant than males. Blood urea and serum creatinine levels too were noted to be slightly higher in patients with microalbuminuria as compared to those who did not have microalbuminuria diabetic retinopathy was seen in 25% of patients with microalbuminuria. Microalbuminuria was associated with abnormal HDL levels but normal LDL levels. A total of 7.5% patients who had microalbuminuria had an increased serum cholesterol level and 22.5% were noted to have an increased triglyceride level.

INTRODUCTION

Diabetes mellitus is one of the most common endocrine disorders and is characterized by metabolic abnormalities along with long-term microvascular and macrovascular complications. The prevalence of diabetes in developing countries is on the rise. It not only multiplies the risk of coronary artery disease, it also increases the incidence of cerebrovascular accidents, end stage renal failure, blindness and also non traumatic limb amputations.

The aim of this study was to study the occurrence of microalbuminuria in patients with newly diagnosed non-insulin dependent diabetes mellitus and also to find out it its association with increased BMI, lipid profile and glycated hemoglobin levels.

Aims: To screen newly detected diabetes mellitus type 2 patients for the presence of microalbuminuria.

Objectives: To study the prevalence of microalbuminuria in newly detected diabetes mellitus type 2. To study the severity (by grading) of microalbuminuria in newly detected diabetes mellitus type 2. To start ARB/ACE inhibitors in patients with microalbuminuria to prevent its further progression.

Literature review: The main pathological features of diabetic kidney disease occur in the glomerulus. Glomerulus consists of tuft of 20-40 capillary loops, which arise from an afferent and drain into an efferent arteriole. Mesangial tissue, comprising both the cellular and matrix components, support lobules of capillaries. Electron microscopy of the loops shows that each loop consists of a basement membrane lined by fenestrated endothelium and covered by visceral epithelial cells (podocytes) carrying foot processes that interdigitate along the membrane, leaving spaces (filtration slits or pores) between the processes. The Bowman“s capsule

encloses the glomerular tuft, which is continuous with the tubular basement membrane and binds the urinary space. Filtration of the plasma proceeds from the capillary, across the endothelium (probably via the fenestrae) and the basement membrane, through the slit pores of the epithelium into the urinary space and the proximal tubule (Tisher, 1981).

In diabetes, the volume of the whole kidney and of individual glomeruli is increased at the time of diagnosis and glomeruli continue to enlarge later (Drummond and Mauer, 2002; White and Bilous, 2000) in the disease. Early glomerular enlargement is probably due to enhanced basement membrane production leading to an increased in filtration surface area while later expansion may be caused due to mesangial expansion (Phillips *et al*., 2001). The increase in total renal volume is likely to be caused by tubular tissue.

In diabetic nephropathy, renal size is therefore usually normal or large even when end stage renal failure develops, which is in contrast to most causes of chronic renal failure in which renal size tends to decrease with advancing disease. In some cases however, concomitant renal artery stenosis or upper urinary tract infections may contribute to a reduction in overall renal size (Hostetter 2001). Basement membrane thickening has long been recognized as a pathological hallmark of diabetes (Thomson *et al*., 2004). Thickening can be detected within two (Osterby *et al*., 2001) years of the detection of diabetes mellitus. Marked thickening occurs in patients with diabetes for duration >10 years (Vestra *et al*., 2001). Mesangial expansion seems to occur after the thickening of the glomerular basement membrane, although this may not be the true sequence of events because it is technically easier to detect changes in basement membrane thickness than in the mesangium (Sharma *et al*., 2003; Osterby 1992). Matrix accumulation rather than cellular increase accounts for most mesangial expansion (Steffes *et al*., 1992). Unlike basement membrane thickening, mesangial volume may be normal in some patients after 25 years of diabetes, although , those with established nephropathy invariably have mesangial 23 expansion. Nodular lesions consisting of ovoid accumulations of Periodic Acid Schiff (PAS) positive material, often occupying the central mesangium of a lobule, is almost pathognomonic of diabetes (Morley *et al*., 1988). When progressed, these changes are known as the Kimmelstiel-Wilson kidney. Hyaline deposits also occur as eosinophilic, a cellular material but are non-specific and are found in several other renal conditions. They can be present inside Bowman's capsule (capsular drop), between the endothelial cell and basement membrane (fibrin cap) and in the afferent and efferent arterioles. Global glomerular sclerosis or occlusion, caused by mesangial expansion or ischemia secondary to afferent arteriolar blockage, is a feature of patients with declining GFR (Kim and Cheigh, 2001). As in other types of progressive renal disease, the tubules and interstitium may show a variety of non-specific (Morley *et al*., 1988; Kim and Cheigh, 2001) changes. The observation of higher arterial pressure in microalbuminuric patients without reduced GFR speaks against the assumption that higher blood pressure is consequence of renal dysfunction and argues in favor of more complex relationship. This raises the possibility that the rise in blood pressure could be contributory to renal disease or alternatively that microalbuminuria and higher blood pressure may be related to a common determinant. It is of interest that microalbuminuric patients with elevation of arterial pressure show significantly more marked mesangial expansion than do patients with lower AER and arterial pressure. There is overwhelming evidence linking hyperglycemia to diabetic micro vascular and macro vascular complications. In the kidney, histological changes such as mesangial expansion may be reversed by transplantation of diabetic kidney in to a normal animal or by correcting diabetes with islet cell transplantation. Chronic over expression of growth hormone or growth hormone releasing factors may lead to early glomerular enlargement followed by glomerulosclerosis. Growth hormone, insulin like growth factors, TGF-B, PDGF and other growth promoters may trigger mesangial cell proliferation and increase in mesangial matrix synthesis (and/or decrease its degradation), so causing pathognomonic features of diabetic glomerulopathy (Greene, 1988).

Diabetes induces important metabolic, hormonal and growth factor changes. These changes that are related in part to the degree of glycemic control, occur in virtually all patients, but till now it has been impossible to isolate a subset of individuals in whom the severity of these environmental perturbations is convincingly linked to development of these complications.

Microalbuminuric diabetic patients have also been found to have higher sodium-lithium counter transport activity. Higher rate of counter transport were associated with elevated LDL cholesterol, total and VLDL triglycerides and reduced HDL cholesterol concentrations. The mechanism of association between sodium lithium counter transport activity, hypertension and lipid abnormalities and susceptibility to diabetic renal and vascular disease could be insulin resistant state.

These associations (i.e., albuminuria, left ventricular and renal hypertrophy and insulin resistance) were independent of actual level of blood pressure or duration of arterial hypertension. This combination of risk factors may not be confined to diabetic population but may be a manifestation of syndrome in general population (Syndrome X) (Brownlee, 2001; Morocutti *et al*., 1992; Rosskopf *et al*., 1993). Sodium-hydrogen antiporter is a

cell membrane cation exchanger that catalyses the electroneural exchange of extracellular sodium ions for intracellular hydrogen ions with a stociometry of 1:1. Molecular ionic studies have so far revealed the presence of five subtypes of sodium hydrogen exchangers (Poczatek *et al*., 2000).

The kidneys are of usually normal size. They may be enlarged in the early stages but later becomes contracted with granular surface. The cut surface is usually pale and the renal arteries may show arteriosclerosis later stages. In our study we have used Micral test for estimation of microalbuminuria. Micral test (Boehringer Mannheim, Germany) is dipstick method of estimation of microalbuminuria. Test principle is immunochemical in nature. Sensitivity of Micral test was 93% and its specificity was 93% when compared to radioimmunoassay in a study by Gilbert *et al*. (1997). Micral test has also been compared with immunoturbidimetric assay and radioimmunoassay methods. In all studies Micral test is comparable in sensitivity and specificity to the other methods of estimation of microalbuminuria. A detailed cardiovascular examination is necessary early in the course of diabetic nephropathy. Hypertension must be treated energetically. Left ventricular hypertrophy and function should be assessed echocardiographically at the stage of microalbuminuria and thereafter every 6-12 months. Effective antihypertensive therapy can reverse left ventricular hypertrophy. In addition, cardiac assessment should include electrocardiography, stress testing, coronary angiography and Holter monitoring is indicated whenever needed. Ischemic heart disease should be treated aggressively. Peripheral vascular disease must be assessed and treated as necessary. Doppler flow studies and arteriography may be useful to assess the severity of the disease (Rutter, 1999; Care, 2000).

Microalbuminuria is frequently associated with hyperlipidemia and lipid profile is an essential investigation and dyslipidemia should be treated (Battisti *et al*., 2003). Testing vibration perception threshold and thermal discrimination may identify the risk of neuropathic ulceration. The test should be repeated regularly as sensation may become impaired later, during the course of nephropathy. Autonomic dysfunction is very common in nephropathy patients. The important manifestations are postural hypotension and incomplete bladder emptying which predisposes to urinary tract infection (Szelag *et al*., 1999). Microalbuminuria is frequently associated with retinopathy. Retinopathy almost always accompanies diabetic nephropathy. Early and regular ophthalmic review and prompt treatment is necessary to prevent blindness (Masoud *et al*., 2003; Ozmen and Boyvada, 2003).

MATERIALS AND METHODS

The 120 patients of Newly Diagnosed Diabetes Mellitus type 2 (NIDDM) admitted to the tertiary care centre were screened. The patients were taken from the wards of the hospital. The classic symptoms of diabetes mellitus include polyuria, polydipsia, polyphagia, unexplained weight loss, non healing wounds, recurrent urinary tract infections, vaginal candidiasis, etc.

RESULTS AND DISCUSSION

The data was entered in MS Excel spread sheet and was analyzed using SPSS Version 20 and Epi info Version 7.2. Levene's Test for Equality of Variances was used and equal variances were assumed within the groups. Independent sample test (Unpaired t test) was used to test equality of means. Chi square test was used to test significance of qualitative variables. $p<0.05$ was considered as significant.

In our study population of 120 patients, the maximum of 53 (44.2%) patients were from 51-60 years of age, followed by 28 (23.3%) patients which were in the 61-70 year age group, 22 (18.3%) patients were in the age group of 41-50, 9 (7.5%) patients were in the age group of 30-40, 5 (4.2%) patients were in the range of 71-80 and 3 (2.5%) patients were above the age of 80 (Table 1). In our study, population of 120 patients, 69 (57.5%) patients were males and 51 (42.5%) were females (Table 2).

Among the study population, 72 (60%) patients tested negative for urine microalbumin while the remaining 48 (40%) tested positive. Among them, a major portion of 31 (25.8%) patients diagnosed were 1+ for urine microalbumin at the time of testing while 11 (9.2%) patients were 2+, 5 (4.2%) patients were 3+ and 1 (0.8%) patient was 4+ (Table 3).

There was a significant increase in HbA1c levels in females (9.35 g%) as compared to males (8.49%). 47.5% patients HbA1c was between the range of 7.5-10,

Table 1: Age wise distribution of patients

Age (Years)	No. of patients	Percentage
30-40	9	7.5
41-50	22	18.3
51-60	53	44.2
61-70	28	23.3
71-80	5	4.2
>80	3	2.5
Total	120	100.0

Table 2: Gender wise distribution of patients

Sex	No. of patients	Percentage
Females	51	42.5
Males	69	57.5
Total	120	100.0

Table 3: Grading of microalbuminuria among the study population

Microalbuminuria	No. of patients	Percentage
-	72	60.0
+	31	25.8
++	11	9.2
+++	5	4.2
++++	1	0.8
Total	120	100.0

while 25.8% patients levels were between 10-12 and 1.7% of patient's levels were noted to be in the range above 12. Thus there was noted to be a significant relation between poor glycemic control and microalbuminuria. In our study, population of 120 patients, 40 patients were noted have abnormal urinary glucose levels and microalbuminuria while 45 patients having abnormal urinary glucose were not noted to have microalbuminuria. This study has also brought out a significant association of microalbuminuria with body mass index of >25 kg m^{-2}. The mean BMI (26.10) was significantly higher in patients with microalbuminuria. About 30 patients from our total study population were noted to be pre obese and 9 were noted to be obese. It is a well known fact that retinopathy and microalbuminuria go hand in hand. In our study group 10 (25%) out of 40 patients were noted to have retinopathy along with microalbuminuria.

CONCLUSION

The incidence of microalbuminuria is estimated to be 40% in this study. Microalbuminuria shows a direct relationship with increasing age of patients. HbA1c value above 7% is associated with 50% or higher incidence of microalbuminuria. Patients with a body mass index of >25 kg m^{-1} increase in the incidence of microalbuminuria have significant. Incidence of microalbuminuria is significantly associated with presence of coronary artery disease and retinopathy. Microalbuminuria also has a significant relation with HDL, poor glycemic control and body mass index.

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