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STUDY OF RENAL AND LIPID PROFILE IN DIABETIC PATIENTS

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ABSTRACT

Background: Diabetes mellitus is one of the most challenging health problems of 21st century and has become a global health problem. With the increase in incidence of diabetes it is inevitable that diabetic nephropathy will also become a major problem. The earliest clinical detectable stage for diabetic kidney disease is Microalbuminuria. Methods: Total 102 diabetic patients were enrolled and biochemical estimations including blood glucose levels, lipid profile, serum creatinine, blood urea, urine routine examination, microalbumiuria and histopathologic study of kidney biopsy wherever possible was conducted. Results: Type 2 Diabetes was far more common than type 1 diabetes. Prevalence of microalbuminuria was 41% and equal in both sexes. Increasing age, duration of diabetes, glycemic control, blood urea and serum creatinine are important risk factors for the development of Microalbuminuria but there was no significant association between sex and lipid profile with development of microalbuminuria. We found a high incidence of pyuria in diabetic females. Conclusion: Renal Parameters like Blood urea and serum creatinine were higher in patients with positive microalbuminuria. Hence, microalbuminuria can be used as rapid screening test for early detection of diabetic nephropathy. A high prevalence of dyslipidemia was present in all diabetic patients. This needs to call for a strict lipid control in diabetic patients to prevent complications.

KEY WORDS

Diabetes mellitus, Microalbuminuria, Renal parameters, Lipid profile

INTRODUCTION

Diabetes mellitus (DM) is one of the most challenging health problems in the 21st century. It is affecting millions of peoples, about 6-7% of the world's population.[1,2] Type 2 DM constitutes about 85% to 95% of all DM cases. If preventive measures are not taken, it is estimated that 438 million people will have diabetes by 2030. India leads the global top ten in terms of the highest number of people with diabetes, with a figure of 50.8 million for 2010.[3]

Less glycemic control, smoking, high blood pressure, elevated cholesterol levels, obesity, and lack of regular exercise are considered to be risk factors that accelerate the deleterious effects of diabetes.[2,4,5] DM is associated with a greater risk of mortality from cardiovascular disease which is mainly due to dyslipidemia.[6]

One third or more of the DM patients develop Diabetic Nephropathy (DN) with progressive deterioration of renal function and structure in their life time.[7, 8] DN is the leading cause of end-stage renal disease (ESRD) worldwide. The earliest clinical evidence of DN is the appearance of low but abnormal levels (30 to 300 mg/day) of albumin in the urine, referred to as Microalbuminuria.[9,10]

Without specific interventions, 20–40% of type 2 diabetic patients with Microalbuminuria progress to overt nephropathy.[11]

Since renal complications are very common in diabetics, we studied the renal profile in diabetics. Blood urea and serum creatinine are the simplest way to measure the kidney function. These substances accumulate in the body in cases of renal dysfunction thus raising their levels in the body.

Kidney biopsy is not carried out as a routine diagnostic test in DN. It is done to confirm or exclude non diabetic kidney disease.[12]

MATERIALS AND METHODS

This study was conducted in diabetic OPD and indoor patients of a tertiary care hospital. A total of 100 patients of type 2 diabetes and 2 patients of type 1 diabetes were included in the study.

Patients with acute illness, pregnancy, recent exercise within 24 hours prior to test, malignancy, renal stones or patients in whom albumin of post-renal origin was present were excluded from this study.

Microalbuminuria was estimated using the immunoturbidimetric method using random spot urine sample, blood sugar levels by GOD-POD (glucose oxidase peroxidase) end point method, blood urea nitrogen by GLDH (glutamate dehydrogenase) urease method, serum creatinine by Jaffe's method and lipid profile using enzymatic end point method.

Routine Urine examination was done in a random spot sample and analyzed for protein, sugar, blood, pus cells and RBC's. More than 5 leucocytes per high power field were considered as pyuria.

Kidney biopsies were fixed in formaline, paraffin blocks were prepared after standard tissue processing. The slides were cut and stained with haematoxyline and Eosin (H&E), periodic acid Schiff (PAS) and Jone's silver methanamine stains to study the histopathologic features. Direct immunoflourescence (DIF) was done on biopsies sent in phosphate buffered saline wherever possible. Immunoflourescenece was done using Ig G, Ig A, Ig M, C3.

RESULTS

A total of 100 cases of Type- 2 diabetes and 2 cases of Type 1 diabetes were studied. Out of total 100 Type II diabetes patients there were 56 males and 44 females. The male to female ratio is 1.27:1. The age of the patients ranged from 21 years to 80 years. The mean age of patients was 55 years.

Glycemic control has been shown to prevent nephropathy. Glycemic status of the subjects from the present study is given in Table 1. Males have higher values of fasting and post prandial blood sugar levels than the females indicating poor glycemic control which is an indicator of diabetic nephropathy.

Table 2 gives the lipid profile of the diabetic patients. The female diabetics had significantly higher triglyceride (TG), LDL-C and high-density lipoprotein cholesterol (HDL-C) values as compared to male diabetics. Based on ATP III classification, as shown in Table 3 we observed a high prevalence of dyslipidemia. About 40% and 43% of the subjects had elevated levels of total cholesterol (TC) and TG respectively. An alarmingly high 56% of the subjects had LDL-C levels higher than 100 mg/dl. Low levels of HDL-C were seen in 52% of the diabetics.

We also studied the renal function parameters like blood urea and serum creatinine in diabetics (Table 4). Both serum creatinine and blood urea were higher in males as compared to females. This could be correlated with high blood sugar levels in males.

Table 5 gives the biochemical characteristics in normoalbuminuric and microalbuminuric subjects. Fasting blood sugar, blood urea and

serum creatinine were significantly higher in the microalbuminuric group. Lipid profile parameters were not significantly different in both the groups.

Table 6 shows the overall prevalence of microalbuminuria is 41% out of which 21 are males and 20 are females. The mean age for positive microalbumin is 57 years and for negative Microalbumin is 51 years. As the duration of diabetes increases the amount of protein excretion also increases. Patients with more than 15 years of duration of diabetes have protein excretion of 3+ and 4+. On the other hand patients with diabetes duration less than 5 years have mainly either normal albumin excretion or Microalbuminuria. So there is a positive relationship with duration of diabetes and protein excretion.

We also studied the relationship of sex, age, duration of diabetes and lipid profile with Microalbuminuria. Sex and lipid profile parameters had no significant association with positive Microalbumin ($p > 0.05$). On the other hand patients above 51 years of age and duration of diabetes more than 5 years and less than 10 years had a positive significant association with Microalbuminuria ($p<0.05$).

The prevalence of pyuria in Type 2 diabetic females in present study was 56%. It was observed that as the age, duration of diabetes and protein excretion increases the chances of pyuria also increases.

A single renal biopsy of Type 2 diabetes patient was studied to look for the renal involvement in a 40 year old male patient with history of hypertension and ischemic heart disease since 6 months. There was no history of nephropathy or retinopathy. Urine examination was done.Urine Albumin was 3+, RBCs - 6-8/HPF and 24 hrs protein was 3.4 gm. Serum Creatinine 6.3mg/dl which increased rapidly from 4.8 over 1 month. Nodular Diabetic Glomerulosclerosis was observed on histopathologic examination. [Figure 1, 2]

We found only 2 cases of Type 1 diabetes. Both the cases were females and in the age group of 14 to 15 years. Renal biopsy was performed in one of the cases to look for the renal involvement.

Renal biopsy was indicated due to presence of proteinuria in association with short diabetes duration, rapid decline of renal function and absence of diabetic retinopathy.

The patient was 14 year old female with diabetes of duration 4 years and associated hypertension of 4 years duration. Blood and urine investigation was done. Blood urea was 132mg/dl and serum creatinine was 7.2mg/dl. Urine albumin was 3+, sugar-3+, RBC - 1-2/HPF.

Histopathologic examination showed core renal tissue with up to 12 Glomeruli of which 11 were sclerosed, remaining showed matrix expansion and thickening of capillary wall, moderate to marked tubular atrophy, interstitial fibrosis and hyaline casts. [Figure 3]

DIF showed linear staining of capillary wall with IgG. IgA, IgM and C3 were negative. Advanced Diabetic Nephropathy was the final diagnosis given.

Table 1: Glycemic status in Type 2 DM

BSL (mg/dl)	Male (n=56)	Female (n=44)	Total (n=100)
Fasting	165 ± 47	155 ± 52	161 ± 49
Post-Prandial	259 ± 68	241 ± 87	251 ± 77

Table 2: Lipid profile in Type 2 DM

Lipid Profile (mg/dl)	Male (n=56)	Female (n=44)	Total (n=100)
HDL	41 ± 10	46 ± 8*	44 ± 8
LDL	92 ± 28	110 ± 34*	101 ± 24
TG	132 ± 35	171 ± 81*	149 ± 62
TC	184 ± 46	196 ± 43	161 ± 37

Data are Mean±SD, *p<0.05

Table 3: Prevalence of Dyslipidaemia in Type 2 Diabetes Mellitus

Lipid profile (mg/dl)	Males (n=56)	Females (n=44)	Total (n=100)
TC ≥ 200	24	19	43
TG ≥ 150	24	16	40
LDL ≥ 100	25	31	56
HDL<40	37	15	52

Table 4: Kidney functions in Type 2 DM

Kidney Parameters (mg/dl)	Male (n=56)	Female (n=44)	Total (n=100)
Blood Urea	37 ± 28	33 ± 26	35 ± 27
Serum Creatinine	1.92 ± 2.43	1.26 ± 1.18	1.62 ± 1.99

Data are Mean ± SD

Table 5: Biochemical Characteristics in Normoalbuminuric & Microalbuminuric group

Biochemical Parameters (mg/dl)	Urine Albumin <30 µg/ml (n=25)	Urine Albumin ≥30 & <300 µg/ml (n=41)
BSL Fasting	151 ± 28	164 ± 21*
BSL PP	228 ± 72	259 ± 77
HDL	44 ± 9	42 ± 9
LDL	104 ± 34	98 ± 31
TG	147 ± 40	149 ± 58
TC	192 ± 47	188 ± 44
Blood Urea	26 ± 8	38 ± 30*
Serum Creatinine	0.99 ± 0.17	1.84 ± 2.27*

Data are Mean±SD.
Significantly different from Normoalbuminurics *p<0.05

Table 6: Duration of Diabetes and Protein excretion in Type 2 DM

Duration (years)	Mean Age	<30 µg/ml	>30 & <300 µg/ml	1+	2+	3+	4+	Total
0-5 Years	54	22	27	8	3	1	0	61
5-10 years	52	1	10	7	0	1	0	19
10-15 Years	59	2	4	5	2	2	1	16
> 15 Years	65	0	0	0	0	2	2	4

Figure I: Glomerulus showing a. KW lesion (black arrow) (H&E X400), b. KW lesion (black arrow) and thickening of the basement membrane (red arrow) (PAS, X 400)

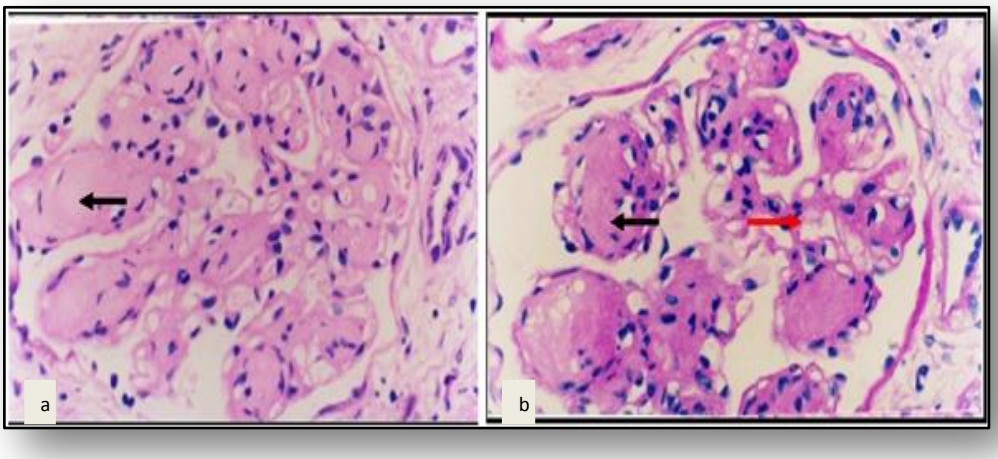


Figure II: Jones stain showing increase in glomerular basement membrane thickening. (Jones, X400)

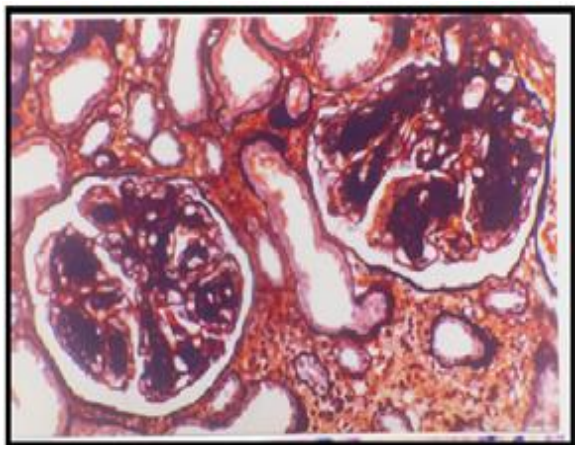
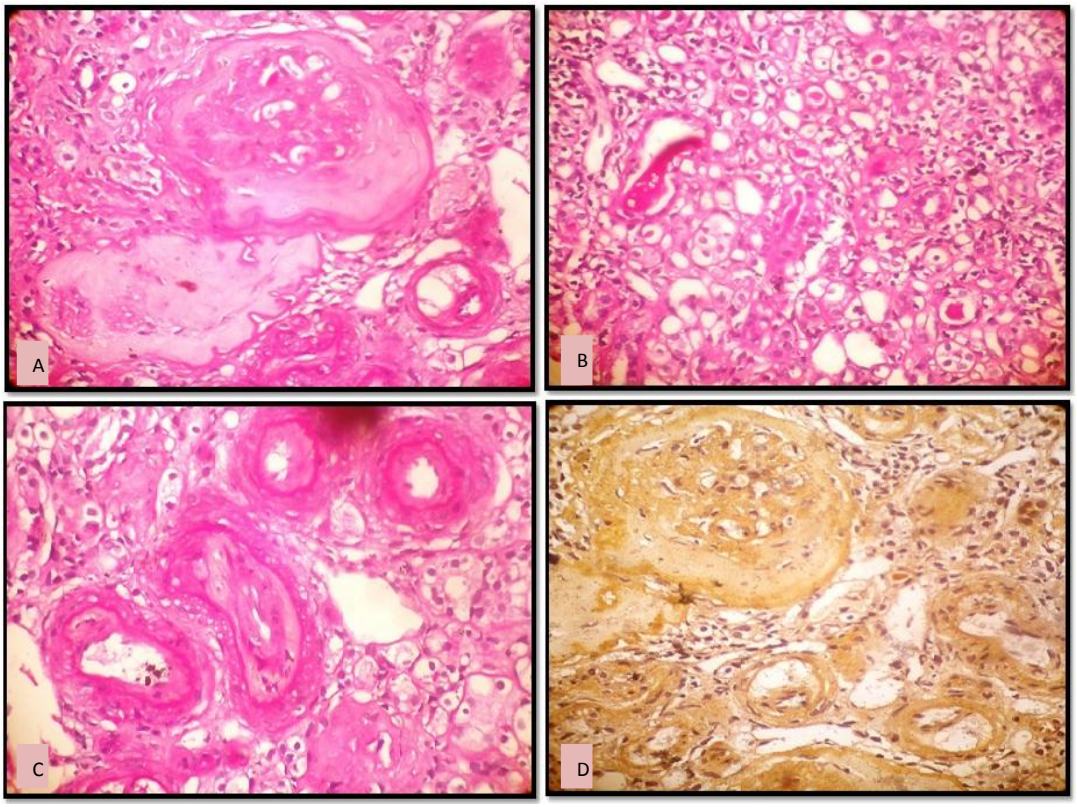


Figure III: Kidney biopsy of Type I DM showing A. Crescent formation and completely sclerosed Glomerulus is seen [H&E, 400X], B. Tubular atrophy, thyroidisation and chronic interstitial inflammation [H&E, 100X], C. Hyaline arteriosclerosis of the renal vessels [H&E, 400X] D. Glomerular basement membrane thickening and tubular basement membrane thickening seen [Jones silver methanamine stain,400X].



DISCUSSION

In our study we found that type 2 diabetics outnumbered the type 1 diabetic cases. We found only 2 cases of type 1 diabetic as compared to 100 cases of type 2 diabetics.

It has been previously reported that Type II diabetes accounts for 90-95% and Type I accounts for 5 -10% of all diabetic cases.[2]

Males have higher values of fasting and post prandial blood sugar levels than the females in our study indicating poor glycemic control in males which is an indicator of diabetic nephropathy. Strict glycemic control lowers the risk of nephropathy and of other diabetic complications.

We also observed that the female patients had significantly higher values of triglyceride, total cholesterol, HDL and LDL as compared to male diabetics.

Several factors are likely to be responsible for diabetic Dyslipidaemia: insulin effects on liver apoprotein production, regulation of lipoprotein lipase, actions of cholesteryl ester transfer protein, and peripheral actions of insulin on adipose and muscle.[13]

There are many other theories proposed to account for the excess risk of diabetes in women. These include differences in coagulation, the pattern of obesity between men and women, and possible role for hyperinsulinemia. Diabetes may

also alter oestrogen related protective mechanisms. Furthermore, low grade inflammation may have a greater role in perturbing insulin action in women, or inflammatory factors may interact with female sex hormones, resulting in a decrease of protective effects of estrogens on body fat distribution and insulin action.[14]

We studied the kidney function parameters like serum creatinine and blood urea. Both serum creatinine and blood urea were higher in males and in patients with positive Microalbuminuria. This can be explained and co related with poor glycemic control in both these groups. In our study group few patients with diabetic nephropathy and few who were on dialysis had very high values of serum creatinine and blood urea and this was the reason behind significantly high standard deviation of the values of blood urea and serum creatinine.

Over time, high blood sugar levels damage millions of nephrons - tiny filtering units within each kidney. As a result, kidneys are unable to maintain the fluid and electrolyte homeostasis. Creatinine is filtered by the Glomerulus; therefore, serum creatinine level is used as an indirect measure of glomerular filtration. As glomerular filtration rate (GFR) diminishes, there is a rise in plasma concentrations of serum creatinine and urea. Furthermore, this rise indicates progression of diabetic nephropathy and estimation of serum creatinine has greater prognostic ability compared with urea for predicting the adverse outcomes.[15]

Therefore, raised serum urea and creatinine levels in diabetics clearly indicate that prolonged hyperglycaemia causes irreversible damage to nephrons of kidney. Raised serum creatinine and reduced GFR has become firmly entrenched as fairly reliable indicators of kidney dysfunction.

The overall prevalence of Microalbuminuria in our study was 41%. Increasing age, duration of diabetes, glycemic control, blood urea and serum creatinine are important risk factors for the development of Microalbuminuria but there was no significant association between sex and lipid profile with development of Microalbuminuria. There was no significant difference in lipid profile of normoalbuminuric and Microalbuminuric patients. Our findings are similar to the findings reported in other studies.[16,17,18]

The prevalence of pyuria in Type 2 diabetic females was 56%. The risk factors include increasing age, duration of diabetes and macroalbuminuria. Our findings are consistent with the findings of Geerlings et al.[19]

We observed that pyuria and bacteriuria is a complication of diabetes in women. Endothelial dysfunction, oxidative stress, and the increased formation of advanced glycosylation end products may play a role in the development of diabetic complications. These factors may also contribute to the development of infections because these factors can lead to disturbances in monocyte migration and cytokine and chemoattractant production.

Diabetes causes unique changes in kidney structure. Classic Glomerulosclerosis is characterized by increased glomerular basement membrane width, diffuse mesangial sclerosis, hyalinosis, microaneurysm, and hyaline arteriosclerosis. Tubular and interstitial changes are also present. Areas of extreme mesangial expansion called Kimmelstiel-Wilson nodules or nodular mesangial expansion are observed in 40–50% of patients developing proteinuria.

The criteria for renal biopsy are not well established, but in type 1 diabetes the presence of proteinuria in association with short diabetes duration and/or rapid decline of renal function, especially in the absence of diabetic retinopathy is considered as an indication for renal biopsy. In

patients with type 2 diabetes, the criteria are less clear.[20]

On average, diabetic nephropathy was the most common pathology in proteinuric patients with type 2 diabetes mellitus (64.8%), followed by non-diabetic kidney diseases (18.7%), normal renal structure (13.2%) and non-diabetic nephropathy superimposed on diabetic nephropathy (3.3%).[12]

We found only two cases of renal biopsy since renal biopsy is routinely not performed in diabetic patients. It is indicated however in patients where non diabetic renal disease is suspected. This was limitation of our study.

CONCLUSION

Given the high speed increase in the prevalence of diabetes in India, our findings suggest the use of Microalbumin to retard the development of renal and cardiovascular complications in type 2 diabetics. Therefore there is a need to propagate the importance of monitoring biochemical and biophysical parameters amongst diabetics. We feel that, all diabetic patients should routinely monitor their glycemic status, renal and lipid profile to avert micro and macro- vascular complications associated with diabetes mellitus.

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