Original Research Article

Correlation of microalbuminuria with neuropathy in type-II diabetes mellitus patients

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ABSTRACT

Background: The microvascular and macrovascular complications in diabetes mellitus resulting in microalbuminuria and diabetic neuropathy in common in developing country like India. The aim of the study has been undertaken to emphasis upon the association of microalbuminuria with neuropathy.

Methods: The study was undertaken among 124 Type-II diabetes patients in the Department of Medicine, VIMSAR, Burla, Odisha between October 2015 to September 2017. Detail history, clinical examination, BMI, laboratory investigation like FBS, PPBS, HbA1C, nerve conduction study was done, and data were analysed and compiled.

Results: Out of 124 patients the mean age of male patients in the study was 49.75 years and that of female patients was 50.36 years. The mean age of the study population was 50.18 years. The mean BMI in patients with and without microalbuminuria was $23.95 \pm 2.04 kg/m^2$ and $21.57 \pm 2.89 kg/m^2$ respectively. The mean HbA1C value in patients with and without microalbuminuria was 9.96 ± 3.380 and 8.75 ± 3.25 respectively.

Conclusions: Microalbuminuria is significantly associated with presence of neuropathy. The most common type of neuropathy observed in this study was distal symmetrical sensory motor neuropathy. Hence, microalbuminuria has an important role as a biochemical marker for risk factor evaluation of microvascular complications in type 2 diabetes mellitus.

Keywords: BMI, Diabetes mellitus, HbA1C, Microalbuminuria, Neuropathy

INTRODUCTION

Diabetes mellitus is one of the most common endocrine metabolic diseases. The microvascular and macrovascular complications, resulting in nephropathy, retinopathy, neuropathy, and ischaemic heart disease has been emphasized.

Microalbuminuria is commonly associated with other microvascular complications of diabetes namely retinopathy, neuropathy, and ischaemic heart disease. So, microalbuminuria may be used as a clinical biochemical marker to look other for widespread microvascular damage in a patient of diabetes mellitus.[1] Microalbuminuria significantly increase in albumin excretion rate (AER). Albumin excretion. Microalbumimuria defines the wide substantial range of albumin hypersecretion ranging between 20 to 200mcg/min (30 to 300mg/day).[2,3]

The presence of microalbuminuria precedes the development of overt diabetic nephropathy by 10-15 years. Therapeutic interventions which reverse microalbuminuria include intensified insulin administration, dietary protein restriction. Diabetic neuropathy is next common complication of Diabetes mellitus. It is generally considered to be related to duration and severity of hyperglycemia. Nerve conduction study shows-abnormal conduction, predominantly demyelinating type of neuropathy.

Conduction velocity slowly decreases as duration of diabetes increases and directly related to blood sugar levels, conduction velocity improves with HbA1c levels returning to normal.

METHODS

This study was conducted at Department of Medicine, VIMSAR, Burla, Odisha between period October 2015 to September 2017. The study included 124 patients of Type-II DM, newly diagnosed Type-II DM. Details history related to diabetes were taken and detail clinical examination done and study of complications of diabetes.

Inclusion criteria

- Type 2 diabetes mellitus patient on treatment
- Newly diagnosed patients of type 2 diabetes mellitus.

Exclusion criteria

- Chronic kidney disease
- Pregnancy
- Inflammatory bowel disease
- Liver disease
- Malignancy
- Type 1 diabetes mellitus.

The following investigation were done

Microalbuminuria was estimated by Micral test in all cases. Glycolated haemoglobin (HbA1C) done by glycohaemoglobin analyzer. Test done by auto analyzer are- fasting blood sugar, Postprandial blood sugar, Blood urea and creatinine, Serum sodium and potassium, Serum cholesterol, Urine routine and microscopy, Nerve conduction study (NCS) done by EMG (Electromyography) sensory NCS done by F-wave study, motor NCS by H-reflex study.

Statistical analysis

The Statistical software namely SPSS 11.0 and Systat 8.0 were used for the analysis of the data. Microsoft word and Excel have been used to generate Figures and Tables.

Student T test has been used to find the significance of mean levels of lab parameters between the presence and absence of microalbuminuria. Fisher's exact test has been used to study the significance of association between microalbuminuria and neuropathy, also to study significance of association between microalbuminuria and smoking habit. 2 tailed P-value of less than 0.05 has been considered to be significant

RESULTS

It is a prospective study consisting of 124 type 2 diabetes mellitus patients is undertaken to investigate the of

microalbuminuria and its relationship with neuropathy in patients of type 2 diabetes mellitus.

Table 1: Duration of type 2 diabetes mellitus since diagnosis.

Duration of diabetes mellitus	Male (n=70)		Female (n=54)		Total N-124
	No.	%	No.	%	No.
≤ 5 year	39	55.71	27	50.00	66
6-10 year	24	34.28	23	42.59	47
Mean duration of diabetes mellitus	7	10.00	4	7.40	11
	5.38		5.41		5.34

Table 2: Number of patients with microalbuminuria in relation to age.

Age in years	Microalbuminuria				Total
	Present		Absent		
31-40 years	7	21.87%	25	78.12%	32
41-60 years	36	51.42%	34	48.57%	70
61 years	17	77.27%	5	22.73%	22
Total	60		64		124
Mean±SD	54.67±9.79		45.97±10.19		50.18± 10.88

P-value-0.0001

In Table 2 32 patients were in the age group between 31 and 40 years, among which 18 were male and 14 were female. 70 patients were in the age group between 41 and 60 years among which 39 were male and 31 were females.

22 patients were in the age group of 61 years among which 13 were male and 9 were female. The mean age of male patients in the study was 49.75 years and that of female patients was 50.36 years. The mean age of the study population was 50.18 years.

Table 3: Association of the duration of type 2 Diabetes mellitus since diagnosis with incidence of microalbuminuria.

Duration of DM	Microalbuminuria				Total
	Present		Absent		
≥years	22	33.33%	44	66.67	66
6-10 years	27	62.79%	20	37.21	47
11 years	11	100%	0	0%	11
Total	60		64		124
Mean ±SD	7.33±4.13		3.47± 2.39		5.34±3.86

p-value-<0.0001

In Table 3 66 patients had duration of diabetes since diagnosis ≤5 years among which 39 were male and 27 female patients. 47 patients had duration of diabetes since diagnose is between 6-10 years among which 24 were male and 23 were female patients. 11 patients had duration of diabetes since diagnosis ≥11 years among Which 7 were male and 4 were female patients. The mean

duration of diabetes since diagnosis was 5.38 years among the male patients and 5.41 years among the female patients.

Table 4: Association of smoking with microalbumin smoking and microalbuminuria.

Microalbuminuria	Smoker/Non- smoker		Total
	Smoker	Non-smoker	
Present	26 59.09%	34 42.5%	60
Absent	18 40 .90%	46 7.5%	64
Mean ±SD (mg/lt)	36.18± 25.69	27.53± 23.09	30.59± 24.31

P-value 0.0575

In Table 4 of 124 patients, microalbuminuria was present in 60 patients and absent in 64 patients. Among the 32 patients in the age group between 31-40 year, 7 had microalbuminuria. 70 patients were in the age group between 41-60 years among which 36 patients had microalbuminuria. 22 patients were in the age group 61 years among which 17 patients had microalbuminuria. The mean age of patients with and without microalbuminuria was 54.67±9.79 and 45.97±10.19 yrs respectively. This suggest for an increase in the incidence of microalbuminuria with age as denoted by significant p-value (<0.0001).

Table 5: Association of BMI with microalbuminuria.

Body mass index (Kg/m^2)	Microalbuminuria		
	Present	Absent	Total
<18.0 (Underweight)	0 0%	4 100%	4
18-22.9 (Normal weight)	12 24%	38 76%	50
23-24.9 (Over weight)	30 66.67%	15 33.34%	45
25 (Obese)	18 72%	7 28%	25
Total	60	64	124
Mean ±SD	23.95 ±2.04	21.57 ±2.89	22.72 ±2.78

P-value-<0.0001

In Table 1 the number of patients with the duration of diabetes since diagnosis ≤5 years were 66 and among them 22 were positive for microalbuminuria. The numbers of patients with the duration of diabetes since diagnosis between 6-10 years was 47 and among them 27 were positive for microalbuminuria. The number of patients with the duration of diabetes since diagnosis 11 years were 11 among them all were positive for microalbuminuria. The mean duration of diabetes since diagnosis in patients with and without microalbuminuria was 7.33±4.13 years and 3.47±2.39 years respectively. This shows that incidence of microalbuminuria increases with duration of diabetes as suggested by significant p-value (<0.0001).

In Table 4 of 60 patients with microalbuminuria, 26 patients were smokers and 34 were non-smokers. The mean AER (albumin excretion rate) in smoker and non-smoker was 36.18±25.69mg/l and 27.53±23.09mg/l respectively. This study showed no correlation of smoking with microalbuminuria (p-vaLue-0.0575).

In Table 5 BMl <18.0 kg/m^2 mg/dl among 4 patients, out of which none had microalbuminuria. BMI between 18-22.9 kg/m^2 was present in 50 patients out of which microalbuminuria was present in 12 and absent in 38 patients 45 patients had BMI between 23-24.9 kg/m^2 of which microalbuminuria was present in 30 cases and in the were absent 15 cases.

Out of 25 patients with BMI ≥25 kg/m^2 microalbuminuria was present in 18 cases and absent in 7 cases. The mean BMI in patients with and without microalbuminuria was 23.95±2.04kg/m^2 and 21.57±2.89kg/m^2 respectively. This shows a significant association of increasing BMI with microalbuminuria (<0.0001).

Table 6: Fasting blood sugar with microalbuminuria.

Microalbuminuria			
≤126 mg/dl	5 26.31%	14 73.68%	19
≥126mg/dl	55 52.38%	50 47.61%	105
Total	60	64	124
Mean ±SD	153.75+17.1	139.75+15.90	146.56+17.85

P-value-<0.0001

In Table 6 19 patients had FBS ≤126mg/dl out of which, microalbuminuria was present in 5 subjects and absent in 14 subjects. Of the 105 patients with FBS >126nig/dl, microalbuminuria was present in 55 subjects and absent in 50 subjects. Of 42 patients with PPBS<140mg/dl, microalbuminuria was present in 14 patients and absent in 28 patients.

Table 7: Association of post prandial blood sugar with microalbuminuria.

Post prandial blood sugar	Microalbuminuria		
	Present	Absent	Total
≤140 mg/dl	14 33.33	28 66.67	42
≥140 mg/dl	46 56.09%	36 43.90%	82
Total	60	64	124
Mean ±SD	180.36±43.02	149.63±25.03	164.5±38.03

In Table 7 82 patients with PPBS ≥140mg/dl, microalbuminuria was present in 46 patients and absent in 36 patients. The mean FBS in patients with and without microalbuminuria was 153.75±17.1 mg/dl and 139.79±15.90mg/dl respectively. The mean PPBS in patients with and without microalbuminuria was 180.36±43.02mg/dl and 149.63±25.03mg/dl respectively. This shows a significant correlation between microalbuminuria and blood sugar level (p-value <0.0001).

In Figure 1 33 patients had HbAIC values less than 6.5% and among them 11 were positive for microalbuminuria. 34 patients had HbA1C values between 6.5-8.0% and among them 18 were positive for microalbuminuria. 57 patients had HbA1C values more than 8.0% and among them 31 were positive for microalbuminuria. The mean HbA1C value in patients with and without microalbuminuria was 9.96±3.380 and 8.75±3.25 respectively. Incidence of microalbuminuria increases with rise in HbA1C as denoted by significant p-value of 0.04.
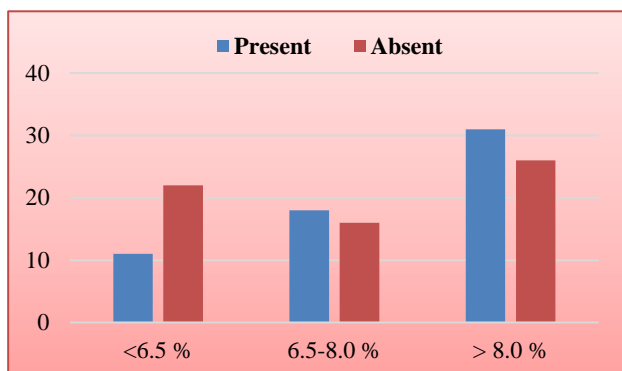
Figure 1: Association of HbA1C with the incidence of microalbuminuria.

In Table 8 112 patients had serum cholesterol <200mg/dl out of which microalbuminuria was present in 55 patients and absent in 57 patients. Of 12 patients with serum cholesterol value ≥200mg/dl, microalbuminuria was present in 5 patients and absent in 7 patients.

Table 8: Association of serum cholesterol with microalbuminuria.

| Serum cholesterol	Microalbuminuria				Total
	Present		Absent		
<200 mg/dl	55	49.10%	57	50.89%	112
200 mg/dl	5	41.67%	7	58.33%	12
Total	60		64		124
Mean±SD	160.71 ±22.71		165 ±25.15		163.35 ±24.03

P-value-0.25

The mean serum cholesterol level in patients with and without microalbuminuria was 160.77±22.71mg/di and

165±25.15mg/dl respectively. This study did not show any increase in incidence of microalbuminuria with rise in serum cholesterol level as denoted by p- value of 0.25.

Out of 56 patients had peripheral neuropathy among which microalbuminuria was present in 50 patients .68 patients had no peripheral neuropathy among them 10 were positive for microalbuminuria. The mean AER (albumin excretion rate) in patients with and without peripheral neuropathy was 47.71±27.08 and 16.5±5.99 mg/I respectively. Incidence of microalbuminuria increases with peripheral neuropathy as denoted by p-value of <0.0001.

In Figure 2 51 patients with peripheral neuropathy, 29 patients (51.78%) had distal symmetrical sensory motor neuropathy, 20 patients (35.71%) had distal symmetric sensory neuropathy, 5 patients (8.92%) had asymmetrical proximal motor neuropathy and 2 (3.57%) had diabetic mononeuropathy. This study shows that distal symmetric sensory motor neuropathy was the most common type of diabetic neuropathy.
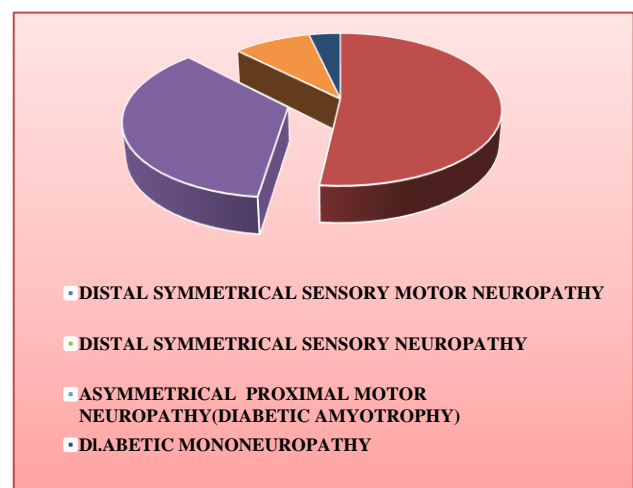
Figure 2: Types of diabetic neuropathy.

DISCUSSION

In our study done on randomly selected patients the incidence of microalbuminuria was found to be 48%. In NIDDM patients, the prevalence has been reported in between 8-46% in European and 26- 36% in lndia.[4,5]

Increase in the percentage of microalbuminuria in our study can be attributed to the large number of elderly patients and the long duration of diabetes study found out the prevalence of microalbuminuria to be 54.09% in a group of 61 patients taken for the study.[6]

The prevalence of microalbuminuria to be 25.5% in a population of 800 patients recruited for the study.[7] The prevalence of microalbuminuria in 36.3% of patients in a group of 1425 taken up for the study.[4] 102 patients were enrolled to study the prevalence of microalbuminuria and

it was found to be 28.4%.[8] The prevalence of microalbuminuria to be 50% in 100 subjects taken up for the study.[9]

The mean age of patient in present study were 50.18 years. In present study microalbuminuria was present in 36 out of 70 patients among the age group between 41-60 years which compromises 51% of the total subjects having microalbuminuria. Of the 22 patients in the age group 61 years 17 patients has microalbuminuria. This shows microalbuminuria was twice more common in the age group above 60 years in comparison to the diabetic subjects with age less than 60 years. The mean age of patients with and without microalbuminuria was 54.67±9.79 and 45.97±10.19 yrs respectively. Microalbuminuria was significantly associated with age (p-value<0.0001).

Study on 280 diabetic subjects that microalbuminuria was present with mean age of patients to be 53.27±9.9 years.[10]

Study on 205 patient of type 2 diabetic patients found that mean age in years in micro albuminuric and normoalbuminuric patients were 7±8.7 and 44±8.7 yrs respectively.[11]

Study on 100 patients showed that microalbuminuria was present in cases with mean age of 49.79±10.3 years and in controls with mean age of 47.46±10.5 years. And the correlation of age of onset of diabetes with microalbuminuria was not significant.[12]

Study on 100 patients showed mean age of onset of diabetes mellitus in microalbuminuria patients to be 51.7± 9.8 years and that in normoalbuminuric patients to be 46±11.6 years. Gender wise correlation was not significant.[13]

In present study show microalbuminuria was more common with duration of diabetes more than 6 years. 62% of the study population with duration of diabetes more than 6 years had microalbuminuria. And almost all diabetic subjects with duration of diabetes above 11 years had microalbuminuria. The mean duration of diabetes since diagnosis in patients with and without microalbuminuria was 7.33±4.13 and 3.47±2.39 yrs respectively. This shows microalbuminuria was significantly associated with long duration of diabetes as denoted by significant p-value of <0.0001. Study on 100 patients showed prevalence of microalbuminuria with mean duration of diabetes to be 10.3± 5.93 years.[14]

Study on of 150 patients showed that with duration of diabetes more than 4 years microalbumin levels were 0.449 ± 0.160 g/day.[15]

Study on 280 patients found that prevalence of microalbuminuria was 7.3% with duration of diabetes less than 10 years and 28.1% with duration of diabetes more than 10 years.[5]

Study on 100 patients found mean age of onset of diabetes in microalbuminuric patients to be 10.7±5.6 years and in normoalbuminuric patients was 3.2±2.0 year.[13] In this study, the mean AER (albumin excretion rate) in smoker and non-smoker was 36.18±25.69mg/I and 27.53±23.09 mg/I receptively. This study showed no correlation of smoking with microalbuminuria (p-value-0.0575). Study on 120 non-diabetic subjects comprising of 80 smokers and 40 non-smokers found that smokers had significant higher urinary albumin levels (52.84±46.42mg/1) than non- smokers (19.25±7.77mg/I).[16] Study on 100 subjects, comprising of 75 type 2 diabetes patients with smoking habits and 25 healthy individuals taken as control, the mean urinary albumin in mg/I in controls and smokers with type 2 diabetes was 37.2±1.74 and 78.0±8.46 mg/ltr respectively suggesting a positive correlation.[17] Study on 125 diabetic patients found that out of 83 normoalbuminuric patients 16 were smokers and out of 39 microalbuminuria patients 16 were smokers suggesting a positive correlation of microalbumin with smoking habits(p-value-0 .04).[18]

In present study 72% of subjects with BMI >25kg/m^2 and 66.67% of patients with BMI between 23-24.9 kg/m^2 presented with microalbuminuria. The mean BMI in patients with and without microalbuminuria was 23.95±2.04 kg/m^2 and 21.57±2.89kg/m^2 respectively.

This suggest for a positive correlation between BMI and microalbuminuria (p-value<0.0001). The possible explanation are:

- Increasing body mass index is related to insulin resistance which lead to endothelial dysfunction and microalbuminuria.
- Poor glycaemic control which is due to insulin resistance is also held responsible.

Study on 288 type 2 diabetes patients found mean BMI to be 27.7±4.11 kg/m^2 prevalence of microalbuminuria among patients with BMI <and >25kg/m^2 was 17.9% and 12.9% respectively suggesting no significant correlation.[10] Study on 100 diabetic patients found mean value of BMI 26.43±3.31kg/m^2 with mean value of microalbuminuria (mg/dl) to be 50.39±34.74 suggesting a positive correlation with p-value of <0.024.[14] Study on 100 patients found mean BMI in microalbuminuric patients to be 22.4±6.9kg/m^2 and BMI in normoalbuminuric patients to be 21.67±4.2kg/m^2 finding no significant correlation.[13]

In this study done it was observed that microalbuminuria was present in 52.38% with fasting blood sugar level more than 126mg/dl and in 56.09% with two hours post prandial blood sugar level 140 mg/di. The mean FBS in patients with and without microalbuminuria was 153.75±17.10mg/dl and 139.79±15.90mg/dl respectively. The mean PPBS in patients with and without microalbuminuria was 180.36±43.02mg/dl and 149.63±25.03mg/dl respectively. This shows a levels

significant correlation between microalbuminuria and blood sugar level (p-value <0.0001). This suggest for a tight glycaemic control in all patients presenting with microalbuminuria to prevent its progression to overt nephropathy.

Study on 288 diabetic patients mean FBS was 167±46.5 mg%. Presence of microalbuminuria among patients with FBS < and > 140 mg/di was 13.9% and 14.9% suggesting no significant correlation. 10 Study on 100 subjects found presence of microalbuminuria with FBS< and >120 mg/dl to be 48% and 60% respectively and with 2 hour PPBS >250mg/dl to be 80.6%.[9]

Study on 150 patients values for FBS, 2 Hr PPBS and microalbuminuria in the control group were 91.1±10.01 mg/di, 119.40±21.16mg/dl, 3.28±2.02 mg/I respectively and that in cases· were 174.15±69.74mg/dl, 221.75±74.12mg/dl, 292.95±156.45 mg/I respectively.[15]

In the present study the prevalence of microalbuminuria was 53% with HbA1C value more than 6.5 and 54% with HbA1C value more than 8.0%. The mean HbA1C value in patients with and without microalbuminuria was 9.95±3.380 and 8.75±3.25 respectively.

Albuminuria increase in HbA1C value and significantly related to it (p-value-0.04). Although this is a cross sectional study. Study on 150 patients showed that microalbuminuira was present with HbA1C of mean 7.8±1.72.15 Study on 100 patients showed that microalbuminuria was present with HbA 1C value 9.0614 Study on 102 diabetic found that microalbuminuria was present in patients with HbA1C value of 9.0±1.4 and normal albuminuric patients had HbA1C value of 1±4.1 respectively.[5]

In this study prevalence of microalbuminuria with serum cholesterol < and 200 mg/di was found to 49.10% and 41.67% respectively. The mean serum cholesterol level in patients with and without microalbuminuria was 160.77±22.71mg/di and 165±25.15mg/dl.

Respectively no positive correlation was found between serum cholesterol and microalbuminuria (p-value-0.25). Study on 100 diabetic subjects found presence of microalbuminuria to be 49% and 58.57% with serum cholesterol <220mg/dl and 220mg/dl respectively.[9] Study on 125 diabetic patients found mean serum cholesterol level in normoalbuminuric and microalbuminuric patients to be 190.8±8 and 187±40mg/dl respectively which was not significant.[18]

Study of 56 patients had peripheral neuropathy among which 50 patients had microalbuminuria which comprises around 80% of the patients of diabetic subjects with microalbuminuria. This shows microalbuminuria was significantly associated with peripheral neuropathy (p= 0.0001). The mean albumin excretion in patients with and without peripheral neuropathy was 47.71±27.05 and 16.5±5.99 mg/I respectively.

Study on patients with chronic peripheral neuropathy, 31 with and 24 without retinopathy. The mean albumin excretion rate (AER) was higher in neuropathic patients with retinopathy than in those patients with neuropathy alone (41.2±40.3 vs 18.8±33.2 micrograms/min, P less than 0.01).

Microalbuminuria was significantly associated with retinopathy although almost half of the patients with neuropathy alone had microalbuminuria.[19]

Study on 170 cases having peripheral neuropathy found that 118 (69.4%) subjects had microalbuminuria and in 52 (30.2%) subjects microalbuminuria was absent of the 273 controls taken for the study who did not have peripheral neuropathy 157 (42.2%) subjects had microalbuminuria and 116 (57.5%) had no microalbuminuria. P-value of 0.012.[20]

Study on 80 diabetic patients found 36 patients had microvascular complications of diabetes. The mean microalbumin level in cases (n=50) was 69.52±59.52 and in controls (n=30) was 14.97±8.3 microgram/min respectively. P value was found to be significant i.e. <0.001.[21]

In another study where 72 cases of IDDM patients were studied. It was seen that presence of peripheral neuropathy (34.4% vs 33.3%) were similar in both normoalbuminuric patients and microalbuminuric patients. Patients with peripheral neuropathy had high AER i.e. (15.2± 6.3 microgram/min).[22]

The most common type of neuropathy observed in this study was distal symmetrical sensory motor neuropathy which comprised of 52% of the total 56 patients who presented with peripheral neuropathy. Other types included distal symmetrical sensory neuropathy, diabetic amytrophy and diabetic mononeuropathy. Study found that 72% of patients had Bi-lateral Symmetrical mixed. Predominant distal Involvement was seen in 94% and 16% patient presented with pure sensory symptoms and 12% had pure motor symptoms.[23]

Study on 380 diabetc patients found that 60% of IDDM had neuropathy of which 54% presented with polyneuropathy, asymtomatic and symtomatic carpel tunnel syndrome in 22% and 11% respectively, visceral autonomic neuropathy in 7% and other varieties 3%.

Among NIDDM patients 59% had various neuropathy the individual percent were 45%, 29%, 6%, 5% and 3% respectively.[24] In a study on 50 patients, 84% had distal symmetrical polyneuropathy, 4% had isolated tibial nerve involvement, 8% had pure sensory sural involvement and only 1 patient each of medial nerve involvement.[25]

CONCLUSION

The prevalence of microalbuminuria in this study population was 48.33%. Incidence of microalbuminuria shows a positive correlation with age and duration of diabetes. With HbA1C >6.5 the incidence of microalbuminuria was 53% in the study population. Occurrence of microalbuminuria was found to be 52.38% and 56.09% with FBS> 126mg/dl and PPBS ≥140mg/dl respectively emphasizing a significant association. The study subjects having BMI >24kg/m^2 had a significant association with microalbuminuria. Microalbuminuria is significantly associated with presence of peripheral neuropathy. No positive correlation was found between serum cholesterol level and smoking habits in patients of type 2 diabetes mellitus. Hence, microalbuminuria has an important role as a biochemical marker for risk factor evaluation of microvascular complications in type 2 diabetes mellitus.

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