

Original Research Article


Development of nephropathy in Type II Diabetes Mellitus with norm albuminuria, micro albuminuria, and macro proteinuria

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Abstract

Earlier Diabetic nephropathy was thought to be a rare complication in Type II Diabetic patients. The incidence and prevalence of nephropathy in Type II Diabetes have been under estimated in the past probably because most patients with nephropathy succumbed to cardiovascular disease, even before nephropathy could manifest clinically. The current study was done to screen Type II diabetic patients for micro albuminuria and macro albuminuria, to identify the risk factors for development of nephropathy, and to note association of other micro vascular and macro vascular complications, and compare them with diabetics without proteinuria.

Key words

Micro albuminuria, Norm albuminuria, Macro proteinuria, Type II Diabetes Mellitus, Diabetic nephropathy.

Introduction

Diabetes Mellitus is the commonest metabolic disorder, which occurs in populations at all ages in both sexes. Complications both micro vascular and macro vascular occurs depending on the

duration, type of disease (Type I or Type II), and other associated risk factors and conditions like Hypertension, Dyslipidemias and Smoking. Glycemic control also influences the development of complications. The degree of

glycemic control is directly related to micro vascular complications whereas in the development of macro vascular complications the relation is indirect and small [1].

Diabetic nephropathy is a single most common cause of End Stage Renal disease (ESRD) in India. In Osmania General hospital Diabetic nephropathy accounts for 20% of all cases of chronic renal failure admitted over a period of 10 years from 1982 to 1992 [2].

The incidence and prevalence of nephropathy in Type II diabetes have been underestimated in the past probably because most patients with nephropathy succumbed to cardiovascular disease even before nephropathy could manifest clinically [3].

Diabetic nephropathy (both Type I and Type II) is usually detected when overt proteinuria develops. Unfortunately, detection at this stage is too late as glycemic control or any other intervention cannot reverse the condition and ultimately the patient will develop ESRD.

By using new diagnostic methods to detect urinary albumin excretion (UAE) sub-clinically i.e., detecting urinary albumin excretion in early stages of nephropathy, it is possible to intervene to retard or reverse nephropathy.

Pathogenesis

Definition of proteinuria

- **Normo albuminuria:** albumin excretion less than 30 mg/24 hours.
- **Micro albuminuria:** Urine albumin excretion ranging 20 – 200 micro grams/minute or 30 – 300 mg/24 hours, 2 or 3 times over three samples collected during 1 – 6 months period [4].
- **Macro albuminuria:** UAE ranging 300 – 500 mg/24 hours.
- **Overt proteinuria:** UAE more than 500 mg/24 hours with diabetic retinopathy.

However, recently easy screening methods (MICRAL STRIP TEST) were developed which

can semi-quantitatively detect protein excretion in the Micro albuminuria range with a sensitivity and specificity of around 90%. Persistent micro albuminuria can be screened easily because UAE of 20 mg/liter or more in one single randomly collected urine sample predicts persistent Micro albuminuria with 91% sensitivity and 83% specificity [5, 6].

Determinants of UAE:

- **Intra glomerular capillary pressure.** It results from both systemic blood pressure and pre and post glomerular resistance.
- **Proximal tubular function:** the amount of albumin normally filtered through the glomerulus is most absorbed through the proximal tubule. Defects in the proximal tubular function can increase UAE.
- **Physical exercise:** it stimulates cardiac output, catecholamine and renin secretion and UAE in normal subjects.
- **Urinary tract infections:** Micro albuminuria can be observed transiently during urinary tract infection due to albumin exudation of the urinary bladder.

Associations of proteinuria

Several studies have described positive associations between micro albuminuria and risk factors for renal and atherosclerotic disease. These risk factors are Hyper-Lipidemias [7], increased fibrinogen levels, Hyper-permeability of both small and large vessels [8]. Poor Blood Glucose control [9], Smoking and Alcohol intake [10, 11], some studies indicate micro albuminuria is frequent among alcohol drinkers in general population [12].

A consistent association has been reported by several workers between albuminuria and high level arterial BP [13, 14]. The rise in intra arterial pressure often still falls within accepted normal range, but on average microalbuminuric patients' display BP values that are about 10 mmHg above that of age, sex and duration matched IDDM

patients with normo albuminuria. The relation to BP is independent of other variables such as blood glucose control. Further more changes in BP have been shown to be correlated positively with changes in AER in a two-year prospective study.

Prognostic value of early proteinuria

The Type – I diabetes subjects micro albuminuria predicts diabetic nephropathy. Diabetic nephropathy indicates reduced life expectancy, but these same subjects with proteinuria primarily die from coronary heart disease rather than from renal failure per se.

In Type – II diabetes micro albuminuria predicts premature mortality due to coronary heart disease, cardiac failure or stroke rather than from uremia. Early proteinuria is also independent predictor for premature mortality from cardiovascular events in general population especially in elderly subjects. Micro albuminuria is frequent in essential hypertension where it is associated with left ventricular hypertrophy, which is an independent predictor for premature cardiovascular death [15].

Finally early proteinuria is an independent predictor for both glomerular and cardiovascular diseases. Proteinuria is extremely uncommon in first years after diabetes onset and in children less than 15years of age, supporting the view that micro albuminuria is an early indicator of glomerular disease rather than a marker of susceptibility to it.

Management of early nephropathy

Diabetes mellitus has become a leading cause of ESRD (End Stage Renal Disease) in west with the increasing incidence of nephropathy in NIDDM due to various causes about 40-90% of diabetes related ESRD cases in the west are due to NIDDM.

The burden of managing cases with ESRD at centers with facilities for dialysis and transplant is very high, in countries India where centers for specialized services are scarce. Therefore it is

important to pickup NIDDM patients with early nephropathy and try to halt the progression of the disease.

Strategies for management of early nephropathy:

- **Control of Blood Pressure:** In Type –I and Type-II diabetic patients with Micro albuminuria and hypertension, control of hypertension is associated with decrease in UAE. The drugs preferred to treat hypertension in diabetes are ACE inhibitors, calcium channel blockers and Alpha agonistic due to their neutral or beneficial effect of carbohydrate and lipid metabolism. ACE inhibitors also decrease the intra glomerular pressure and flow by increasing the efferent vasodilatation and decreasing the afferent vasodilatation at the glomerular level. Improves insulin sensitivity Usage of ACE inhibitors in normotensive micro albuminuric IDDM and NIDDM patients was associated with decreased UAE due to its affect on glomerular pressure reduction.
- **Quit Smoking:** It is advisable to quit smoking, as smoking is a risk factor for the development of micro vascular complications and even though there are not many studies associated with proteinuria [11].

Material and methods

All Type II diabetic patients irrespective of duration of diabetes, whose over night urinary samples collected and estimated for protein levels using calorimetric method with sulphosalicylic acid, whose samples negative for proteins with above method screened for micro albuminuria by the micral strip test.

Inclusion criteria

- Type – II diabetic patients,
- Blood urea and serum creatinine within normal range.

Exclusion criteria

- Urinary tract infections ruled out by microscopic and culture sensitivity,
- Congestive cardiac failure,
- Diabetic ketoacidosis,
- History of Non-diabetic renal disease,
- Pregnancy-on-History,
- Patients with overt proteinuria.

After examining 128 consecutive cases of Type – II diabetes mellitus admitted in the hospital, from September 2003 to January 2005, a total number of 48 patients selected for screening remaining 80 patients were excluded under above exclusion criteria. At the end of the study all these 48 patients divided into 3 groups.

- Group A: Patients having normal albumin excretion (less 30 mg)
- Group B: Micro albuminuria (albumin excretion between 30 – 150 mg)
- Group C: Macro proteinuria (protein excretion between 150 – 500 mg)

Total 25 healthy individuals with similar age and sex groups, similar range of BMI were taken as controls and estimated for overnight urinary proteins.

All the above study groups were compared in terms of age, sex, BMI's, smoking, hyper-tension and other micro vascular and macro vascular complications.

The following investigations had been carried out in all the patients.

- Urine - complete urine examination,
- Urine – culture and sensitivity,
- Urine – overnight urinary proteins,
- Urine – 24 hour urinary proteins,
- Urine – Micral test,
- Fasting blood sugar,
- Random Blood sugar,
- Hb A1c,
- Blood Urea,
- Serum Creatinine,
- ECG

Results and Discussion

Diabetic Nephropathy is most common cause of end stage renal disease (ESRD) in the west. Type –II diabetes accounts for 40% – 90% of this burden in the U.S, in India too diabetic nephropathy is a major cause of ESRD with a prevalence of 26% as reported by Chugh, et al., from Chandigarh [16] and 26.7% as reported by Mani, et al., from Chennai [17]. Also Dr. Mani's series of cases diabetic nephropathy was found in 18.7% of all cases of nephrotic syndrome. Vijay, et al. working at another Diabetic Centre at Chennai found 18.7% prevalence of proteinuria [18]. Nephropathy was seen in 18% (23 out of 128) of all diabetics admitted in our medical unit from Sept 2003 to Jan 2005.

In this study 128 consecutive cases of Type –II diabetes admitted in our unit were screened. A detailed history clinical examination and necessary laboratory tests were carried out. From these 80 patients having overt proteinuria, UTI, CCF, other non-diabetic renal disease and pregnancy were excluded.

Total 48 patients were screened for overnight urinary proteins and micral Strip test as for the procedure described earlier. Based on the results the patients were divided in to three groups.

- Group – A Type – II diabetic patients who are having norm-albuminuria (micral test – ve) total 26 patients.
- Group – B Type – II diabetic patients who are having micro-albuminuria (30 to 150 mg) total 14 patients.
- Group – C Type – II diabetic patients who are having macro proteinuria (150 to 500 mg) total of 8 patients.

A detailed clinical analysis of these 48 patients was made and the differences and their implications are discussed.

25 healthy individuals (14 males, 11 females) who are not having other risk factors for proteinuria, having similar age group (mean age of 58.5 + 5), body mass index (mean BMI 24.6) are screened for overnight urinary proteins.

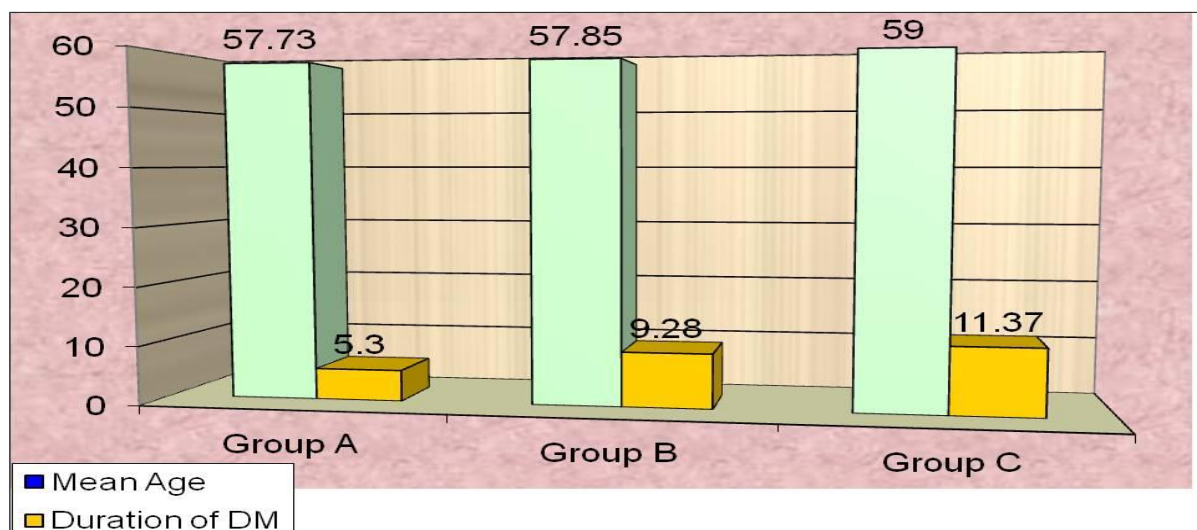
None of the above group found to have micro or macro proteinuria, depicting Sex, Age, BMI are not risk factors for proteinuria.

There was no significant association with mean age, sex and activity with proteinuria in Type –II DM as per **Table – 1** and **Graph – 1**, **Graph - 2**.

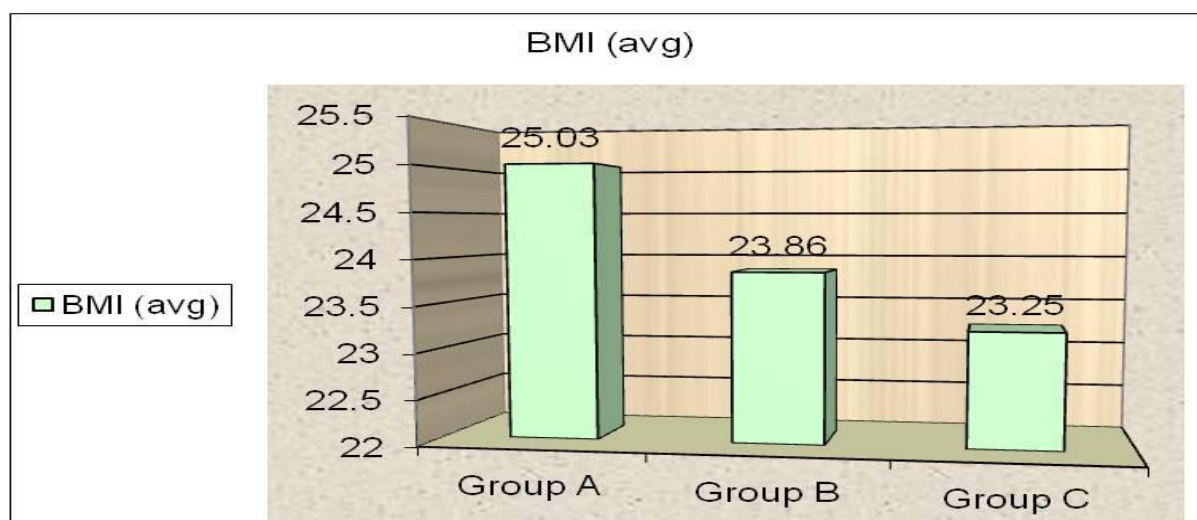
Table – 1: Association of Proteinuria with Sex, Mean Age, BMI.

	Group A	Group B	Group C
No of patients	26	14	8
Sex ratio (Male/ Female)	16/10	9/5	5/3
Mean Age	57.73	57.85	59
BMI (avg)	23.15	23.86	23.25
Sedentary Activity	13 (50%)	9 (64.28%)	4 (50%)
Duration of DM	5.30	9.28	11.37

Graph – 1: Association of proteinuria with Mean age and duration of diabetes.



Graph – 2: Association of proteinuria with BMI.



Duration of Diabetes Mellitus had strong association with development of proteinuria. Proteinuria is seen 7 to 8 years after the onset of Diabetes Mellitus, rarely before 5 years. These observations were similar to the studies done by

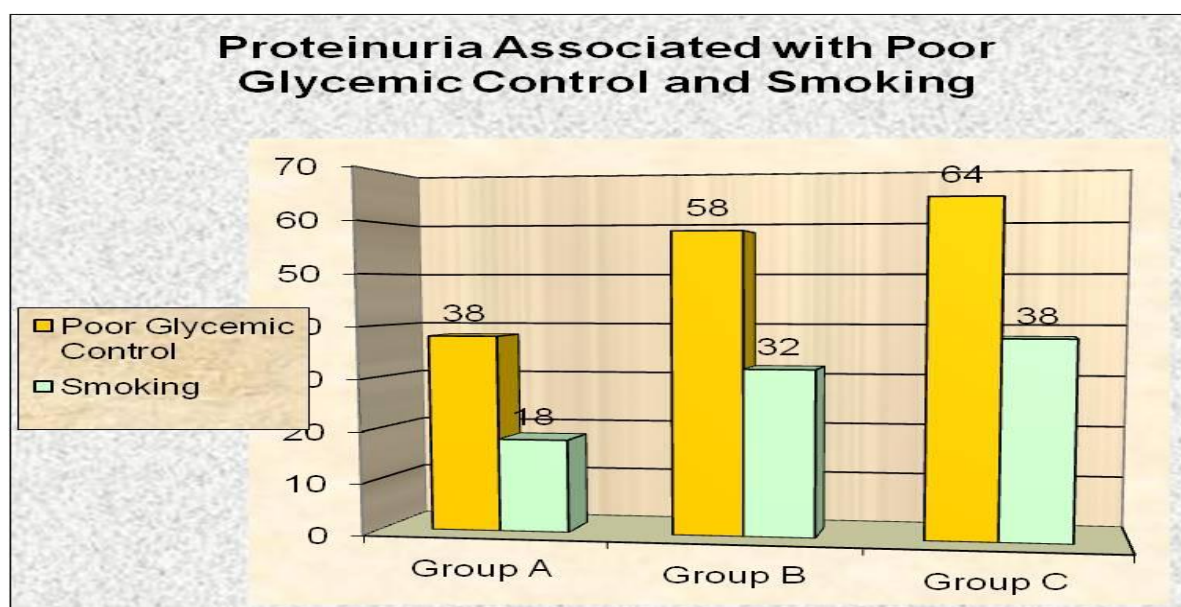
Vishwanathan, et al. in Madras 1995 [19] and Mohan, et al. in Madras 2000 [20].

Poor glycemic control and smoking has shown to be positive association with proteinuria in Type – II diabetes as per **Table – 2** and **Graph - 3**.

Table – 2: Association of proteinuria with poor glycemic control, smoking, family history of DM.

	Group A	Group B	Group C
Poor Glycemic Control	10 (38%)	8 (58%)	5 (64%)
Smoking	5 (18%)	5 (32%)	3 (38%)
Family history of DM	9 (34%)	6 (38%)	4 (32%)
Family history of Nephropathy	0	0	0

Graph – 3: Association of proteinuria with poor glycemic control and smoking.



Till now there are few studies to demonstrate a direct relationship of smoking to proteinuria. Studies done by Nilsson PM, et al. [10], Ikeda Y, et al. [21] concluded smoking as a strong predictor of albuminuria in Type 2 Diabetes. However both smoking and proteinuria are risk factors and risk predictors of vascular disease respectively, it is advisable to stop smoking. This could also be one of the interventions in arresting the progression of diabetic nephropathy.

Our study revealed a strong association of early proteinuria with poor glycemic control. A strong association of poor glycemic control to early

proteinuria in Type –II diabetes was shown in studies by Mogensen, et al [22], and in South Indian NIDDM patients by LilyJohn, et al. [23]. Other South Indian studies predicted poor glycemic control as risk factors for proteinuria are Viswanathan et al from Madras [19], Mohan V, et al. from Madras [20].

The DCCT study also emphasises the role of glycemic control in the prevention and the progression of micro vascular complications in IDDM patients. UKPDS 33 study also showed intensive blood glucose control with sulphonyl ureas or Insulin, in preventing complications in

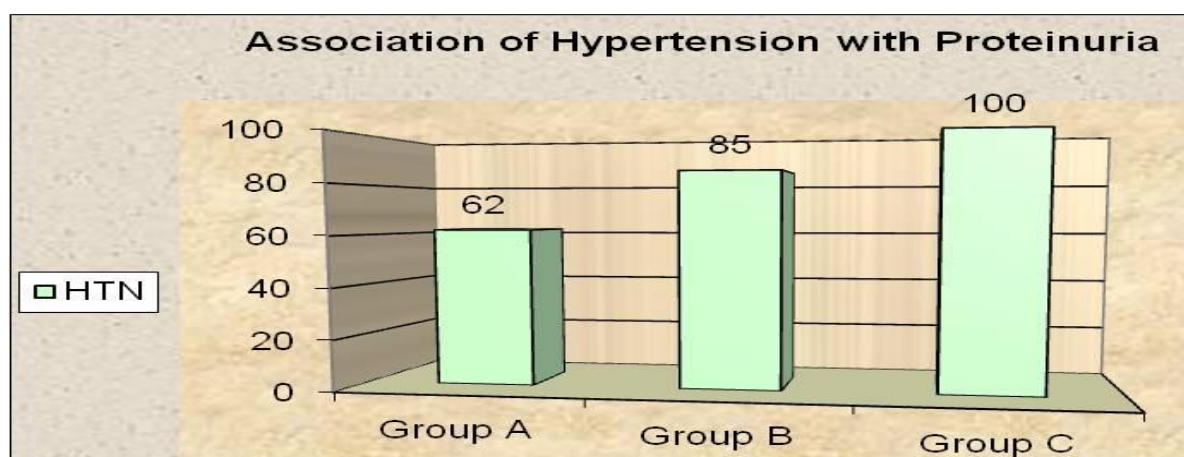
Type 2 Diabetes Mellitus Patients. Hence strict glycemic control will be an important intervention in arresting the progression of early nephropathy. This study did not find any relation with family history of diabetes, or diabetic nephropathy, with early proteinuria in Type – II diabetic Patients. None of our patients recollect family history of Diabetic nephropathy.

The Study Showed high prevalence of hypertension in early proteinuric group as compared to non-proteinuric group as per **Table – 3** and **Graph – 4**. Studies by Mogensen, et al. [22] and Lily john, et al. [23] also shown that mean Blood Pressure is high in early proteinuric Type –II diabetic patients.

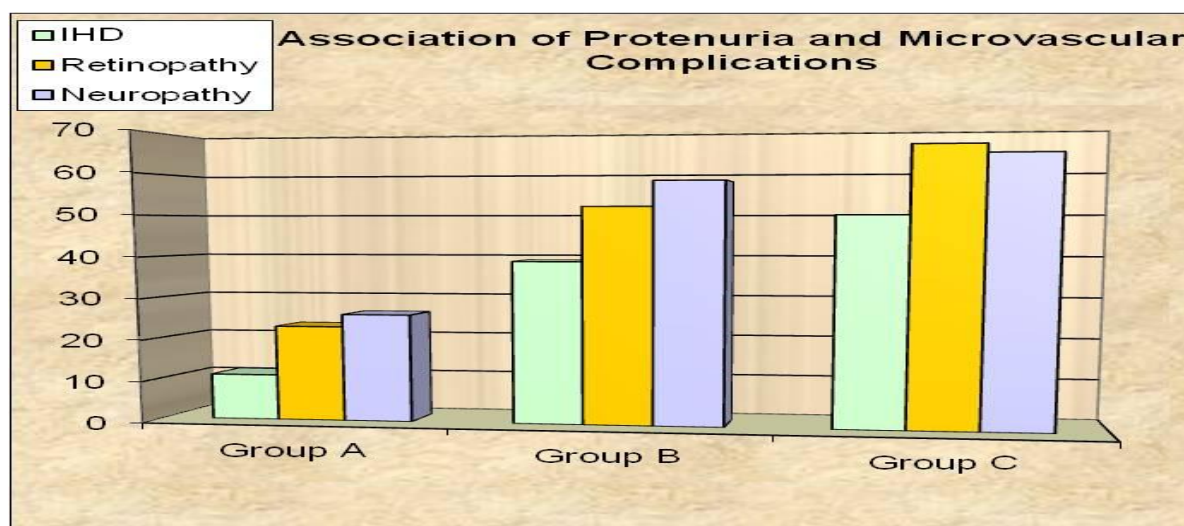
Table – 3: Proteinuria and Microvascular complications in Type 2 DM.

	Group A	Group B	Group C
HTN	16 (62%)	11 (85%)	8 (100%)
IHD	3 (11%)	5 (39%)	4 (50%)
Retinopathy	6 (23%)	7 (52%)	5 (66%)
Neuropathy	7 (26%)	8 (58%)	5 (64%)

Graph – 4: Association of hypertension with proteinuria.



Graph – 5: Association of proteinuria and micro vascular complications.



Most of these patients developed hypertension after a significant time after detection of diabetes. The mean duration of hypertension in micral positive group was 2.8 years, macro proteinuric group is 4.6 years compared to mean duration of diabetes 9.8 years in micro proteinuric group and 11.37 years in macro proteinuric group.

The prevalence of ischemic heart disease was also higher in early proteinuria groups compared to non- proteinuric group as per **Table – 3** and **Graph - 5**. This observation was similar to that of mentioned in PREVEND study [24] and another study done by Rutter MK, et al. [25] regarding incidence and significance of silent Ischemia in micro albuminuric Type 2 DM patients.

This observation showed that micro albuminuria and macro albuminuria are not only an indicator of early nephropathy, but also an indicator of diffuse vascular disease and predictor of cardiovascular deaths.

This study showed significant association of retinopathy in early proteinuric group compared with non-proteinuric group. Retinopathy was mostly background (more than 75%). In a study by Ravid, et al. [26] in normotensive Type –II diabetic patients with micro albuminuria prevalence of retinopathy was 26%, while studies by Eggersten, et al. revealed a prevalence of 40% [27] and prevalence of 34% mentioned by Mohan

V, et al from Madras [20]. This observation emphasises the need to careful monitoring of retinopathy in all cases of early proteinuria and vice-versa. The presence of diabetic retinopathy serves as a marker for diabetic nephropathy, and helps in distinguishing diabetic from non-diabetic nephropathy.

Neuropathy is also a major micro vascular complication. In our study neuropathy predominantly sensory and peripheral was found in 58 and 64% respectively in micro and macro proteinuric Type – II diabetic patients. In a study by Dyck, et al. in Mayo clinic 59% had some form of neuropathy in NIDDM patients with micro albuminuria [28].

Cerebrovascular disease was seen with equal frequency in all three groups. Similarly there was no significant difference in prevalence of peripheral vascular disease in all these three groups. This showed early proteinuria didn't have any significant association with macro vascular complications in Type –II diabetic patients as per **Table – 4** and **Graph - 6**. These observations are similar to studies done by Mohan V, et al. from Madras (1999), showing no significant difference in frequency of peripheral vascular disease in Proteinuric from Non-proteinuric group [20] and peripheral vascular disease appears to be less common among Indian type II Diabetes Mellitus patients compared to Europeans [29].

Table – 4: Association of Proteinuria with Macrovascular complications.

	Group A	Group B	Group C
CVA and TIA	7 (25%)	2 (16%)	3 (22%)
PVD	3 (11%)	2 (16%)	1 (12%)

Group A patients (Normo albuminuria group): all the 23 patients both overnight and 24 hours urinary samples are in the range of Normo albuminuria i.e., micral test negative.

Data depicted in **Table - 5** shows in group B patients (micro proteinuria group) all the 14 patients, both overnight and 24 hours urinary samples – Quantitative estimation of proteins are less than 150 mg and all of them are micral test positive with both the samples. Hence, indicating

that in both overnight and 24 hours sample micro albuminuria is in similar range.

quantitative estimation of proteins in both overnight and 24 hours samples were macro proteinuric range except for 2 patients.

In group C patients, as per **Table - 6** (macro proteinuric group), out of 8 patients for

Graph – 6: Association of proteinuria with macro vascular complications.

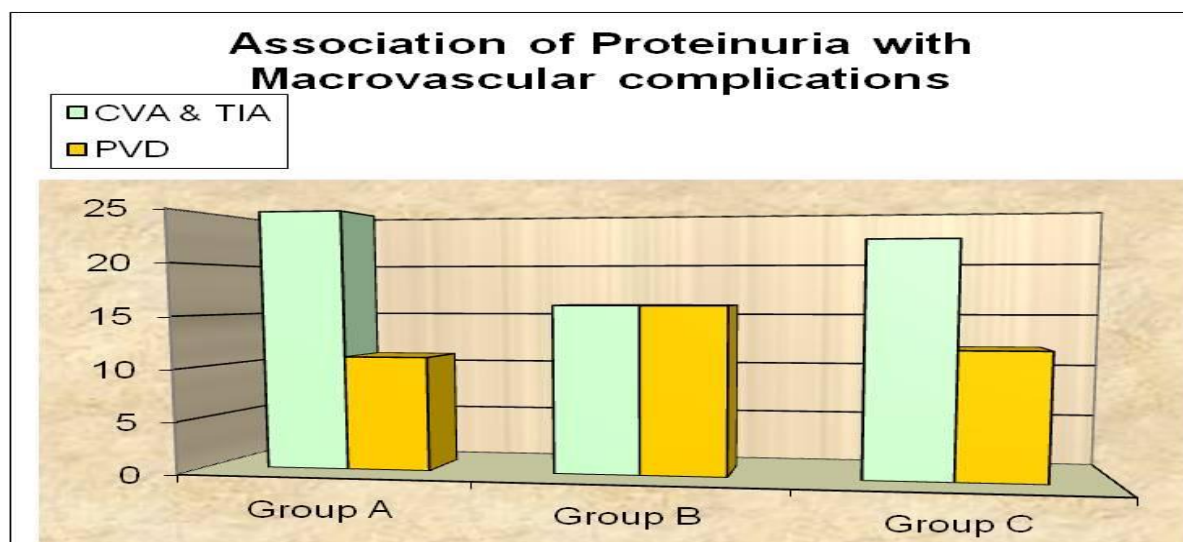


Table – 5: Comparison of overnight urinary samples with 24 hours urinary samples for screening of early proteinuria (Group B Micro proteinuria group).

Pt. No.	Microl Test (mg/l)	Overnight Urinary protein (mg)	24 hours Urinary Protein
1	100	< 150mg	< 150mg
2	100	< 150mg	< 150mg
3	50	< 150mg	< 150mg
4	50	< 150mg	< 150mg
5	100	< 150mg	< 150mg
6	100	< 150mg	< 150mg
7	50	< 150mg	< 150mg
8	100	< 150mg	< 150mg
9	50	< 150mg	< 150mg
10	20	< 150mg	< 150mg
11	50	< 150mg	< 150mg
12	100	< 150mg	< 150mg
13	50	< 150mg	< 150mg
14	100	< 150mg	< 150mg

Table – 6: Comparison of overnight urinary samples with 24 hours. urinary samples for screening of early proteinuria (Group C Macro proteinuria group).

Pt. No.	Microl Test (mg/l)	Overnight Urinary protein (mg)	24 hours Urinary Protein (mg)
1	Negative	380	540
2	Negative	250	280
3	Negative	280	480
4	Negative	320	420
5	Negative	320	360
6	Negative	180	320
7	Negative	500	620
8	Negative	350	480

Over all out of 48 patients screened for early proteinuria using overnight samples and 24 hours samples, except two, remaining 46 samples proteinuria is in similar range in both the samples. (normo, micro, macro proteinuria range) [30, 31].

Hence, overnight urinary samples for screening of early proteinuria are an effective alternate to inconvenient and cumbersome 24 hours urinary collection.

Conclusion

- Age, Sex and physical activity and body mass index do not seem to directly relate to development of early proteinuria in both healthy individuals and Type –II diabetic patients.
- Duration of diabetes seems to be related to development of early nephropathy. However this conclusion has to be interpreted with caution, as the exact time of onset of diabetes cannot be timed in most Type –II diabetic patients.
- Smoking has a strong association with the development of early proteinuria. Hence, discontinuations of smoking will be an important intervention in arresting the progression of early nephropathy.
- Poor glycemic control is also strongly associated with early proteinuria in Type –II diabetic patients. So, tight glycemic control should be aimed at in patients with early nephropathy to prevent development of ESRD.
- Hypertension has a strong association with development of early proteinuria and progression of nephropathy. Hence strict control of Blood Pressure, retards progression of nephropathy, prevents development of ESRD.
- Ischemic heart disease is also common in Type –II diabetic patients with early nephropathy. This association between early proteinuria and Ischemic ECG changes which suggests, that could be an instrument to identify persons with increased risk for coronary disease in an early stage.
- Other micro vascular complications like Retinopathy and neuropathy are having strong association with early proteinuria.
- The macro vascular complications like CVA and peripheral vascular disease are

not seen with any increased frequency in early proteinuria Type – II diabetic patients.

- Overnight urinary protein estimation can be used as an effective alternative for 24 hours urinary proteins estimation for screening of early proteinuria, as 24 hours urine collection is cumbersome and inconvenient to patients and lab staff.

Our study brings the importance of detection of early proteinuria. Such early detection will help in arresting the further progression of nephropathy and prevent the development of end stage renal disease, which is a major cause of morbidity and mortality in Type –II diabetic patients. Moreover early proteinuria predicts development of various micro vascular complications; those can be detected and arrested in initial stages. So while monitoring control of diabetes, screening for early proteinuria should be performed at least once a year, for this screening overnight urinary samples can be used as an effective alternate to inconvenient 24 hours urinary samples.

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