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# Association of microalbuminuria with retinopathy and neuropathy in type-2 diabetic patients

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## Abstract

**Background**: Diabetes is a group of metabolic diseases characterized by hyperglycemia caused by decreased or erratic insulin secretion, insulin action, or both. Diabetes related chronic hyperglycemia is linked to long-term damage, dysfunction and failure of various organs, particularly the eyes, kidneys and nerves which encompass the microvascular com plications of diabetes mellitus. The aim of the study is to find out the Association between these microvascular complications in patients with Type-2 diabetes mellitus.

**Methods:** Cross sectional observational study conducted at a Tertiary Health Care Centre. Patients having diabetes mellitus were screened for micro albuminuria and then were enrolled in the study if found positive. Various biochemical parameters, fundus examination and NCV was performed and co-related. The duration of the study was 2 years.

**Results:** Out of 289 patients who were screened for al buminuria, 81 patients came positive for micro al buminuria with mean age of 59.59 ± 10.18. In which 34 (41.98%) patients had diabetic retinopathy and 24 (29. 63%) patients had diabetic neuropathy. The association of microalbuminuria was compared with retinopathy, neuropathy and duration of diabetes mellitus. There was also positive co-relation between duration of diabetes

mellitus and development of DR and DN. Furthermore, patients having poor glycemic control found to have DR and DN at an earlier stage.

**Conclusion**: Presence of Microalbuminuria can be used as an early indicator for aggressive manage ment of diabetes mellitus to prevent progression to ESRD, DR and DN which possess a significant burden on the society.

**Keywords:** Diabetes, Nephropathy, Fundoscopy, Nerve conduction study, UACR, Peripheral neuropathy

**Introduction**

India is known as the "Diabetes Capital of the World," as every fifth diabetic in the world is an Indian, and it is estimated that six people die from the disease every minute around the world, a figure that will soon make diabetes mellitus as one of the world's most common causes of preventable mortality. [1] Type-2 DM is one of the important type of diabetes accounting for 90% of diabetics in any country.

**It has two types of complication**

1. Microvascular complication (which includes diabetic nephropathy, diabetic retinopathy & diabetic neuropathy)
2. Macrovascular complication (which includes angina pectoris, myocardial infarction, cerebrovascular accident and peripheral vessel disease)

Diabetic nephropathy is a leading cause of chronic renal failure and end-stage renal disease (ESRD) around the world. Approximately 20% of type 2 diabetic patients will develop ESRD during their lifetime. [2] ESRD is caused by a number of factors, one of which is proteinuria, which is a risk factor for renal disease and a predictor of ESRD. [3] In diabetic patients, kidney disease is defined by increasing rates of urinary albumin excretion, starting from microalbuminuria progressing to macro albuminuria and eventually ESRD. [3] Micro albuminuria is the earliest clinically detectable stage of diabetic kidney disease, and it is at this stage that appropriate interventions can slow or stop the disease's progression.

ADA defines micro albuminuria has 30 - 300 mcg albumin/mg creatinine in spot urine. [4]

Diabetic retinopathy (DR) is a micro vascular com plication of diabetes that is a leading cause of blindness and visual impairment. It progresses from mild non-proliferative DR (NPDR) to moderate, severe non-proliferative DR (NPDR) and pro-life rative DR (PDR). Proliferative DR (PDR) is characterized by increased vascular permeability, retinal nonperfusion and pathological intraocular proliferation of retinal vessels. Macular oedema or thickening of the retina, can occur at any stage of retinopathy. [5] If left untreated, this complication places a significant burden on society; thus, early detection and identification of the risks for DR is critical. Glomerular hyperfiltration and proteinuria are known to occur well before overt renal damage or clinically evident diabetic retinopathy. [6] However, the precise level of proteinuria at which early diabetic retinopathy manifests has yet to be determined.

The American Diabetes Association (ADA) defines diabetic peripheral neuropathy (DPN) as "the presence of symptoms and/or signs of peripheral nerve dyes function in people with diabetes after all other causes have been ruled out." [7] Diabetic neuropathy risk is proportional to both the magnitude and duration of hyper glycemia, as with other microvascular complications. This condition is known to be the leading cause of foot ulcers and lower-extremity amputations. [8] About a third of DPN patients experience pain, which has a significant impact on their quality of life. Even though

DPN is the most common diabetes complication, many of its underlying pathophysiological mechanisms are unknown, and targeted therapy is lacking. As a result, early diagnosis and treatment initiation are critical, with early detection likely providing the best chance for effective intervention.

Albuminuria screening is a routine clinical examination that is commonly performed on DM patients upon admission to the hospital. It's also worth noting that once microalbuminuria is present, the creatinine clearance rate in untreated DM patients drops by 10–12 mL/min per year on average. [9] The primary goal of this research is to see if there's a link between diabetic nephropathy and the development of DR and DPN.

**Materials and methods**

It was a cross sectional observational study conducted at Tertiary Health Care Centre, Maharashtra. Every consecutive patient who visits the OPD and/or gets admitted and who fills the selection criteria.

**Inclusion criteria**

1. All consenting adults aged 18 years or above with diagnosis of Diabetes Mellitus (Diagnosed based on WHO criteria) with microalbuminuria (UACR = 30-300 mcg / g).

**Exclusion criteria**

1. Acute febrile illness
2. Heart failure
3. Acute Renal Failure
4. Hyperglycemic crisis (Diabetic ketoacidosis and Hyperglycemic- Hyperosmolar Non-ketoacidosis)
5. Known End Stage Renal Disease patients on Maintenance Hemodialysis
6. Pregnant patients with preexisting DM, Type-1 DM and other rare type of DM
7. Hypertensive crisis, hypertensive emergencies

After ethical committee clearance, every consenting consecutive patient irrespective of gender, having Diabetes Mellitus as diagnosed based on WHO criteria* attending to OPD and/or admitted to Bharati Hospital, Pune were screened for Microalbuminuria. Those patients in whom microalbuminuria was detected were selected and enrolled in the study.

All selected patients were subjected to a detailed history and clinical examination.

HbA1c levels, Serum creatinine and Urinary ACR were done in all subjects.

e-GFR was calculated using the Modification of Diet in renal disease (MDRD) equation.

MDRD formula.

$$\text{eGFR}\left(\frac{\frac{\text{mL}}{\text{min}}}{1.73\text{m}^2}\right) = 175\text{X}(\text{Sr. Creat})^{-1.154}\text{X}\,(\text{Age})^{-0.203}\text{X}742 \text{ if female})$$

Diagnosis of retinopathy was made by doing fundoscopy after full dilatation of pupils. Nerve conduction study (NCS) was done in all patients to confirm the presence of neuropathy clinical parameters like age, duration of diabetes, insulin requirement, presence of other macro vascular complications of diabetes was evaluated.

*WHO criteria for diagnosis of Type II DM:

1. Fasting Blood sugar > 126 mg/dl
2. Postprandial sugar level > 200 mg/dl
3. HBA1C > 6.5 %

**Analysis of results**

SPSS (version 25.0) software was used for statistical analysis. Chi-square test was used to show the association between UACR and diabetic neuropathy. Sensitivity and specificity analysis at various cut offs of UACR was calculated using the Receiver Operating Characteristic (ROC) curve analysis.

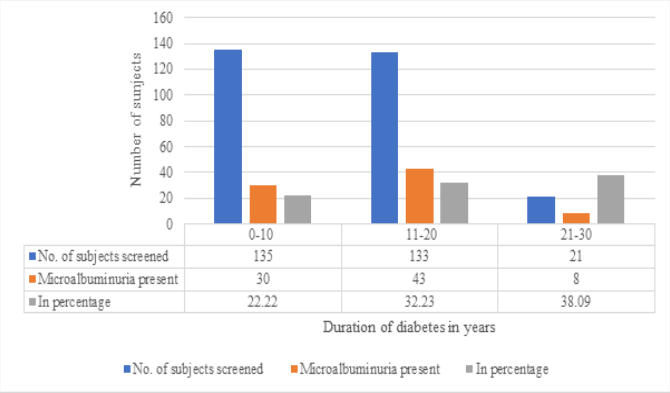
**Results**

Table 1: Demographic details

| | Gender | | |
|---|---|---|---|
| Age in Years | Male | Female | Total |
| 31-40 | 2 | 0 | 2 |
| 41-50 | 8 | 10 | 18 |
| 51-60 | 7 | 13 | 20 |
| 61-70 | 18 | 11 | 29 |
| 71-80 | 4 | 8 | 12 |
| | 39(48.15) | 42(51.85) | 81(100) |

In the present study total of 289 patients who were above the age of 18 years, diagnosed of diabetes mellitus were screened for microalbuminuria. Out of which 81 patients were tested positive for micro albuminuria and 7 patients had macroalbuminuria and the rest 201 were negative for albuminuria. In the subjects who were detected for micro albuminuria, were further followed up for diagnosis of retinopathy and neuropathy. A total of 81 type 2 diabetic patients with microalbuminuria were evaluated with a mean age of 59.59 ± 10.18 years, ranging between 30 to 80 years, and the male to female ratio was 0.93:1.

Figure 1: Distribution of patients as per duration of diabetes mellitus.




In 81 patients with microalbuminuria, 34(41.98%) patients had diabetic retinopathy, 24(patients had diabetic neuropathy and 17 patients had both diabetic retinopathy and diabetic neuropathy.

Figure 2: Findings of fundoscopy

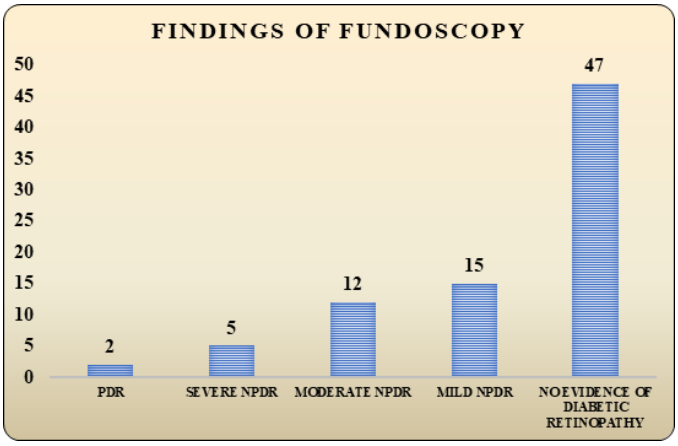



Table 2: NCV specific findings in patients with positive NCV test

| | **Frequency** | **Percent** |
|---|---|---|
| Sensory peripheral neuropathy in both lower limbs | 1 | 4.2 |
| Bilateral lower limbs axonal neuropathy (motor>sensory) | 2 | 8.3 |
| Bilateral sensory-motor predominantly axonal in lower limbs neuropathy | 1 | 4.2 |
| Mild sensory peripheral neuropathy in both lower limbs | 3 | 12.5 |
| Peripheral neuropathy both motor and sensory of lower limbs | 1 | 4.2 |
| Sensory > motor diabetic neuropathy (lower limbs > upper limbs) | 1 | 4.2 |
| Sensory neuropathy in both lower limbs | 6 | 25.0 |
| Sensory-motor polyneuropathy(axonal)lower limbs > upper limbs | 2 | 8.3 |
| Sensory>motor (lower > upper) | 6 | 25.0 |

| | | |
|---|---|---|
| axonal neuropathy | | |
| Severe sensory-motor polyneuropathy (demyelinating = axonal) in both lower limbs > upper limbs | 1 | 4.2 |
| | **24** | **100.0** |

Table 3: Association of presence of class of retinopathy and urine albumin to creatinine ratio

| | **UACR mcg/g** | | **p value** |
|---|---|---|---|
| | **Mean** | **SD** | |
| PDR | 278.00 | 12.728 | <0.001 |
| Severe NPDR | 195.00 | 67.294 | |
| Moderate NPDR | 165.42 | 67.938 | |
| Mild NPDR | 133.27 | 31.189 | |
| No evidence of diabetic retinopathy | 110.89 | 65.369 | |

The mean values of urine albumin to creatinine ratios were calculated according to the class of retinopathy in diabetic patients, and compared between the groups using ANOVA test. There was a significant difference in the mean values of UACR noted between the groups based on class of retinopathy. Further Bonferroni post-hoc test there was significant increase in UACR values in PDR group as compared to patients with mild NPDR (p = 0.022) and no evidence of diabetic retinopathy (p= 0.003). There was also significant increase in UACR in patients with severe NPDR compared to no evidence of diabetic retinopathy (p=0.042).

Table 4: Association of diabetic neuropathy and duration of diabetes

| | | NCV | | Total | p-value |
|---|---|---|---|---|---|
| | | Positive | Negative | | |
| Duration of diabetes | ≤10 | 1 | 29 | 30 | <0.001* |
| | 11-20 | 18 | 25 | 43 | |
| | >20 | 5 | 3 | 8 | |
| Total | | 24 | 57 | 81 | |

The distribution of patients according to NCV and duration of diabetes differ significantly with p value of <0.001

Table 5: Association of neuropathy with class of diabetic retinopathy

| | | NCV | | Total | p-value |
|---|---|---|---|---|---|
| | | Positive | Negative | | |
| Diabetic retinopathy | PDR | 2 | 0 | 2 | 0.0475* |
| | Severe NPDR | 5 | 0 | 5 | |
| | Moderate NPDR | 7 | 5 | 12 | |
| | Mild NPDR | 3 | 12 | 15 | |
| Total | | 24 | 57 | 81 | |

In diabetic patients with microalbuminuria the distribution of patients according to NCV findings and class of diabetic retinopathy as per fundoscopy differ significantly (p=0.0475) with more patients having diabetic neuropathy with increase in severity of diabetic retinopathy.

**Discussion**

With its alarming rise in prevalence, type 2 diabetes has emerged as a pandemic disorder that warrants concern on a global scale. Due to the long course of their illness, these patients have a higher risk of developing long-term complications like diabetic nephropathy, retinopathy, and neuropathy. [10, 11]. It is generally agreed that the first clinical indication of diabetic nephropathy is micro albuminuria. According to Bhavya N [12] et al, micro albuminuria is linked to both neuropathy and retino pathy. We conducted the present study to determine the association between micro-albuminuria with retinopathy and neuropathy in diabetic patients.

Parving HH [13] et al. found a high prevalence of 22% for microalbuminuria, which was later found to be predictive of the onset of diabetic nephro pathy. According to Ahmad T [14] et al., micro al buminuria affects 31.56 percent of diabetics. It is closely related to hypertension, inadequate glycemic control, and other complications like neuro pathy and retinopathy. In our study prevalence of microalbuminuria was 28.02 % in type-2 diabetic patients.

Patients with microalbuminuria were more likely to be older, with a mean age of 64.51 ± 11.47 years, a longer duration of diabetes (8.2 ± 8.4), and higher HbA1c levels (7.56 ± 1.50 %), according to Lee WJ [15] et al. Bariha PK [16] et al, reported that patients with and without micro albuminuria had mean HbA1C values of 9.96 ± 3.38 and 8.75 ± 3.25, respectively. In our present study, mean age was 59.59 ± 10.18 years, ranging between 37 to 78 years, with a mean duration of diabetes of 12.44 ± 5.48 years, and ranging between 2 to 30 years, and the mean level of HbA1c among the study population being 9.17 ± 2.47%.

The progression of microalbuminuria in diabetic nephropathy eventually results in macro albuminuria, which is followed by a gradual loss of glomerular filtration rate (GFR). According to Chen YH [17] et al., the development and progression of diabetic retinopathy is better predicted in patients with type 2 diabetes by microalbuminuria than by a moderate decline in renal function.

In the present study, a total of 34 patients were reported to have evidence of retinopathy, of which non-pro-life rative diabetic retinopathy (NPDR) was more prevalent (39.51%) compared to proliferative diabetic retinopathy (PDR) (2.5%). Among NPDR, 18.5% were of mild type, 14.8% were of moderate type and 6.2% were of severe type. Also, mean UACR differed significantly with higher values in the PDR group as compared to patients with mild NPDR and without evidence of diabetic retino pathy. The findings were similar for the severe NPDR group compared to no evidence of diabetic retinopathy.

Manaviat MR [18] et al. reported a similar incidence of retinopathy (39.3 percent) with some degrees and the distribution according to severity was also comparable for mild (19.2 percent), moderate (12 percent), and severe (2.7 percent) types of NPDR and a relatively high (5.4 percent) rate of PDR. Singh SK [19] et al. found that people with PDR had significantly higher levels of micro albuminuria than people with background retino pathy. According to Lee WJ [15] et al., PDR was present in only 3.8 percent (37/971) of the 194/971 people with retinopathy overall.

Diabetic retinopathy has long been understood to be a micro vascular condition. It is believed that hyper glycemia plays a significant role in the pathogenesis of retinal microvascular damage. The accumulation of AGEs, the protein kinase C (PKC) pathway, the hexosamine pathway, and the polyol pathway have all been connected to hyper glycemia-induced vascular damage. [20]

One of the complications of diabetes is diabetic neuro pathy. It is typically thought to be connected to the length and severity of hyperglycemia. A study of nerve conduction reveals abnormal conduction and primarily demyelinating neuropathy. As the duration of diabetes lengthens, conduction velocity gradually declines. [16] The natural course of diabetic neuropathy and its risk factors are poorly understood, with the exception of the observation that prevalence rises with duration and, in many studies, the degree of glycemia. [21]

Diagnosis of diabetic neuropathy was done using nerve conduction study (NCV) among diabetic patients with micro albuminuria, which was positive in 29.6% of patients. Out of 29.6% of patients with NCV test positive, the most common findings were sensory neuropathy in both lower limbs and sensory>motor (lower > upper) axonal neuropathy, followed by mild sensory peripheral neuropathy in both lower limbs, bilateral lower limb axonal neuropathy (motor> sensory).

Further, most (15) of the patients with positive NCV fell into the group with a DOD of 11 to 20 years, followed by >20 years (5) and ≤10 years (1), with a significant difference. The positive correlation between NCV findings and the class of diabetic retinopathy was significant in diabetic patients with microalbuminuria.

Bell DS [22] et al. reported that diabetic patients with microalbuminuria had a 15% (12/78) incidence of neuropathy. Additionally, a strong correlation was found between microalbuminuria and the side effects of hypertension, ischemic heart disease, neuropathy and retinopathy. When demographic factors were taken into account, neuropathy was only found to be linked to microalbuminuria.

**Conclusion**

There was a strong co-relation between micro al buminuria with retinopathy and neuropathy. Degree of microalbuminuria was co-relating with severity of retinopathy and neuropathy. According to the results of the current study and previous research, people who have micro albuminuria should be considered to be at high risk for developing retinopathy and neuropathy in addition to the increased risk of progression to these conditions.

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