

## Micro albuminuria in type 2 DM- prevalence and its association with microvascular complications

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### Abstract

**Introduction:** Aim of the study was to know the prevalence and association of microalbuminurea with microvascular complication among type II diabetic patients attending tertiary health care.

**Materials and Methods:** Retrospective chart analysis of 375 Type 2 diabetic patients coming to the endocrine clinic at Amrita institute of medical science and research centre Cochin from 2007 to 2012 was done. Randomly selected diabetic patients satisfying the inclusion criteria were selected. Subjects were considered to have microalbuminuria, if the ACR was between 30 and 300, and macroalbuminuria at more than 300. All patients underwent the specific tests for retinopathy, nephropathy, and neuropathy.

**Result:** The prevalence of microalbuminuria in the study subjects was 55.2%. Individuals with microalbuminuria in comparison to normo and macroalbuminurics showed a greater prevalence of diabetic retinopathy and neuropathy. Multivariate logistic regression analysis showed retinopathy as a significant independent risk for microalbuminuria. The average ACR was significantly high in patients with diabetic complications.

**Conclusion:** The estimation of urine albumin to creatinine ratio is an easy method for screening of microalbuminuria that is suggested for all diabetic patients.

**Keywords:** Type 2 diabetes mellitus, Microalbuminurea, Diabetic nephropathy, Retinopathy, Neuropathy.

### Introduction

According to the WHO, diabetes affects more than 170 million people throughout the world, and this figure will rise to 370 million by the year 2030.<sup>1</sup> About one third of these patients affected will eventually have progressive deterioration of renal function. The prevalence of diabetes is on the rise, more alarming is its situation in the developing countries. Besides multiplying the risk for coronary heart disease, diabetes also enhances the incidences of cerebrovascular accidents, which is a debilitating condition for the patient. Moreover it is the leading cause of acquired blindness and accounts for about a quarter of the cases with end stage renal disease as well as half of the cases of non-traumatic lower limb amputations.<sup>1</sup>

The metabolic dysregulation associated with diabetes mellitus causes secondary pathophysiologic changes in multiple organ system. Hyperglycemia promotes the reaction of glucose with components of arterial wall to form advanced glycation products, these products crosslink with collagen which increases the arterial stiffness. The hallmark of diabetic microangiopathy at the level of ultra structural pathology is the thickening of the capillary basement membrane, associated with this is the increased vascular permeability throughout the body which causes the development of micro vascular complications like diabetic retinopathy, neuropathy and nephropathy. The characteristic feature of type 2 DM is that it is often associated with other medical disorders including obesity, hypertension, hyperlipidaemia all of which predispose to micro vascular disease. The collective terminology easily grouped under lifestyle diseases of mankind in the present decade.

Diabetic nephropathy is a dreaded disease with progressive and continuous deterioration in glomerular function resulting in irreversible renal failure. It is an important cause for morbidity and mortality and is also now among the most common cause of end stage renal disease. However there is an early reversible stage of diabetic renal disease called incipient diabetic nephropathy. In this stage there is rise in urinary excretion of albumin, this may mediate the physiological changes which lead to excretion of albumin in the urine known as Albuminurea. Levels of albumin can be expressed as a concentration or as a ratio of albumin to creatinine. But the rise is detectable only by use of sensitive assay for urinary albumin. Microalbuminuria is an established marker of diabetic nephropathy. It begins insidiously and may precede the diagnosis of diabetes. Poor glycemic control is the main fundamental basis for the development of albuminuria and renal lesions. After a few years of duration of diabetes susceptible patients develop intermittent microalbuminuria before having persistent microalbuminuria. The earliest clinical evidence of nephropathy is appearance of low but abnormal level of albumin in urine. To detect the low level human albumin concentration and to study the subclinical increase in urine albumin excretion rate, which is the early pointer to the development of diabetic renal disease.<sup>2</sup> It is in this stage that one can hope to reverse diabetic renal disease or prevent its progression.

Microalbuminuria is associated with significant glomerular pathology and increased level of renal, as well as cardiovascular risks. The increased level of urine albumin secretion may represent a more generalized vascular damage

than the renal micro vascular injury alone. The patterns of progression of renal abnormalities are divided into 5 stages. Stage 1: Thickening of the basement glomerular membrane and accumulation of matrix material.

Stage 2: Nodular deposits and glomerular necrosis as a result protein escapes via glomerular filter.

Stage 3: Insipient diabetic nephropathy – Microalbuminuria.

Stage 4: Overt diabetic nephropathy- Macroalbuminuria. And finally the glomeruli are progressively lost and renal function begins to deteriorate.

Stage 5: End stage renal failure with uremia.<sup>3</sup>

Depletion of phosphoinositidase may result in reduced hydrolysis of phosphatidylinositol bi phosphate and decreased diacylglycerol formation. Diacylglycerol is a major endogenous cellular mediator of protein kinase C activation which itself has been implicated in pathogenesis of diabetic renal disease.<sup>4</sup>

Elevated intraglomerular pressure via increased mechanical stress and shear forces may damage the endothelial surface and disrupt the normal structure of glomerular barrier, and could eventually lead to mesangial proliferation, increased production of extracellular matrix and thickening of glomerular basement membrane. Basement membrane thickening has long been recognized as a pathological hallmark of diabetes.<sup>5</sup> Thickening can be detected within two years of the detection of diabetes mellitus. Marked thickening is seen to occur in patients with diabetes with duration of more than 10years.<sup>6</sup> 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. Matrix accumulation rather than cellular increase accounts foremost mesangial expansion.<sup>7</sup>

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 which also may trigger mesangial cell proliferation and increase in mesangial matrix synthesis, so causing pathognomonic features of diabetic glomerulopathy.<sup>4</sup>

Various previous epidemiological and cross sectional studies<sup>6,7</sup> have reported many variations in prevalence of microalbuminuria. It is well known that diabetic subjects with microalbuminuria not only have ongoing progressive nephropathy but are also likely to have retinopathy, neuropathy and cardiovascular problems including coronary artery disease and hypertension. An effort has been made in this study to highlight this point.

## Materials and Methods

Retrospective chart analysis of 375 type 2 diabetic patients coming to the endocrine clinic at Amrita institute of medical science and research centre was done. Details of duration of diabetes, HbA1c, FPG, PPPG, presence of diabetic retinopathy, nephropathy and neuropathy were collected. Inclusion Criteria included Type 2 diabetic

patients, both male and female, above 30 yrs of age and Type 1 diabetic patients with history of non diabetic renal diseases, presence of active urinary sediments were excluded. The study was approved by the institutional thesis review committee.

Eligible random patients were then randomly selected from the data. HbA1c was done using HPLC and FPG and PPPG using GODPOD method. Nephropathy was diagnosed based on a urine albumin creatinine ratio > 30, Retinopathy based on dilated fundus examination depending on ETDRS classification. Neuropathy using a vibration threshold perception > 25. In our study we have used micro albumin test by immunoturbidometric test for estimation of microalbuminuria. Olympus analyzers automatically compute the albumin concentration of each sample. Microalbuminuria was estimated using ACR with values <30 normoalbuminuric, 30-300microalbuminuric and >300 as macroalbuminuric. The collected data was scrutinized manually before its entry into the computer. Statistical analysis was done using IBM SPSS Statistics 20 Windows (SPSS Inc., Chicago, USA). For all the continuous variables, the results are given in Mean  $\pm$  SD or in Median (Range) and for the categorical variables as percentage. To compare the averages of continuous variables between three groups, those are not following normal distribution, Kruskal-Wallis Test was performed. Chi-square test was used for finding the association between two categorical variables. The p-value <0.05 were considered as statistically significant. All tests of significance were 2-tailed.

In the present work undertaken, the mean HbA1c, FPG, PPPG, duration of Diabetes, retinopathy, nephropathy and neuropathy were studied and correlations were analyzed.

## Results

Our hospital being tertiary referral centre has a good inflow of patients attending the endocrinology department for their lifestyle diseases. It was easily possible to collect the data, and study the data consisting of 375 Type 2 diabetic patients, of which majority of the patients were males (68.8%), and females were (31.2%). The mean ages of the patients were 53.55 $\pm$  9.80 (range 30-82) years. The average age among females is 53.4 $\pm$ 9.60 and among male is 53.62 $\pm$ 9.9 (p=0.842). The prevalence of micro albuminuria in this study was 55.2% (Table 1). The mean micro albuminuria was 64.37  $\pm$  40.35 mcg/min. The incidence of normoalbuminuric diabetic patients was 156 (41.8%), microalbuminuric 206 (55.2%) and macroalbuminuric patients was 11 (2.9%) in the study population (Table 1). There is no significant difference in the incidence of microalbuminuria among male (57.3%) and female (54.3%) patients in this study population. There is no statistically significant difference in the average age among normo micro and macroalbuminuric group of patients. The average duration of the diabetes was 10 years in normoalbuminurics, 10.5 years in microalbuminurics and 12 years in the macroalbuminurics, there is no significant difference in the average duration of Diabetes among the three groups.

(P-Value 0.116)

Amongst the study sample the prevalence of micro vascular complications like retinopathy, neuropathy, and nephropathy were studied and the results obtained were as tabulated in (Table 2).

As compared to normoalbuminuric patients the prevalence of retinopathy in micro and macroalbuminuric showed significant difference. The incidence of retinopathy was high in micro (45.6%) (P-Value=0.006) and macroalbuminurics (63.6%) (P-Value=0.029) than in normoalbuminuric patients (31.4%).

As compared to normoalbuminuric patients the prevalence of neuropathy in macroalbuminuric 11 (100%)

patients showed significant difference (P-Value=0.023). The prevalence of neuropathy in microalbuminurics 154(74.8%) as compared to normoalbuminurics 105(67.3%) showed no significant difference (P-Value=0.120)

Using Multivariate Logistic Regression analysis only retinopathy showed significant independent risk for microalbuminuria.

Microalbuminurics were around 1.78 times likely to have diabetic retinopathy as those without microalbuminuria, P-Value=0.010. Neuropathy (1.353 times) did not show any significant risk for microalbuminurics than normoalbuminurics.

**Table 1: Comparison of ACR of diabetic patients**

|                         | Number     | %    |
|-------------------------|------------|------|
| Normoalbuminuria ≤30    | 156        | 41.8 |
| Microalbuminuria 30-300 | 206        | 55.2 |
| Macroalbuminuria ≥300   | 11         | 2.9  |
| <b>Total</b>            | <b>373</b> |      |

**Table 2: Association of microalbuminuria with microvascular complications**

| Micro vascular Complications | <30 |      | 30-300 |      |       |         | ≥300 |       |       |         |
|------------------------------|-----|------|--------|------|-------|---------|------|-------|-------|---------|
|                              | No  | %    | No     | %    | OR    | p-value | No   | %     | OR    | p-value |
| Retinopathy                  | 49  | 31.4 | 94.0   | 45.6 | 1.833 | 0.006   | 7.0  | 63.6  | 3.821 | 0.029   |
| Neuropathy                   | 105 | 67.3 | 154    | 74.8 | 1.438 | 0.120   | 11.0 | 100.0 | 1.105 | 0.023   |

**Discussion**

Type 2 diabetes mellitus is being increasingly recognized as a disease, which is characterised by dysfunction of the endothelium. Endothelial dysfunction occurs in a generalized and widespread manner in diabetic subjects. The severity of the dysfunction is directly proportional to the age of the patient and duration of the diabetes. The clinical markers of the generalized endothelial dysfunction manifest in several forms. Microalbuminuria marks the onset of endothelial dysfunction related to the kidney. Since the estimation of microalbuminuria is made easy and practical. Microalbuminuria serves as a warning for imminent nephropathy. But its true value is that it heralds generalized endothelial dysfunction.

In this study of Type 2 diabetic patients, the prevalence of microalbuminuria and its association with other complications of diabetes were looked into. We found that the prevalence of microalbuminuria in our Type 2 diabetic population was 55.2%. Microalbuminuria had significant association with microvascular complications namely retinopathy and neuropathy and had no significant association with age, sex, and duration of diabetes.

In our study of randomly selected patients an incidence of 55.2% for microalbuminuria is evident with an average Albumin/Creatinine ratio of 64.37±40.35mg/g. The prevalence of microalbuminurea was slightly higher in this study than the rates of 17 to 21 percent reported from western population based studies in diabetic patients.<sup>8</sup> Observed in various studies from across the continent were as follows- Korea 56.5%, Pakistan 24.2%, Hong Kong.<sup>9</sup> 22.7% and South India.<sup>10</sup> 36.3%.An increase in the

percentage of prevalence of microalbuminuria in this study can be attributed to several factors such as, large number of elderly patients, longer duration of diabetes and poor glycemic control.

In the present study the prevalence of micro albuminuria was not statistically different for the age and sexes male (62.1%), female (67.5%) which was similar to the findings reported by Mather et al. in European diabetic patients.<sup>11</sup> However, Varghese et al. reported an increased prevalence of micro albuminuria in Indian men compared with Indian women.<sup>10</sup> This different prevalence of micro albuminuria between males and females can be due to the lower creatinine excretion in women than in men<sup>11</sup> and the fact that we used the albumin to creatinine ratio to diagnose micro albuminuria. In the present study, no significant correlation was found between the prevalence of micro albuminuria and duration of diabetes that was not consistent with findings of past studies. Varghese et al.,<sup>10</sup> reported a significant correlation between micro albuminuria and the duration of diabetes.

It is very well recognized that microalbuminuria occurs more commonly in diabetic subjects who are more than 50 years of age. In our study microalbuminuria tended to be 2.54 times more common in the age group of above 50 years as compared to the age group of less than 50 years. There are many reasons for this phenomenon. Firstly deterioration in the β-cell function, which occurs parripassu with increasing duration of diabetes, is likely to contribute to worsening glycemic control.

The incidence of retinopathy (45.6%) and peripheral neuropathy (74.8%) was significantly high in

microalbuminurics than normoalbuminurics. We conclude that there is a significant difference in the average ACR between patients with no complication and patients with 1 and 2 microvascular complication. Retinopathy and peripheral neuropathy have significant association with microalbuminuria. This association is not surprising since they are dependent on similar risk factors. Microalbuminurics were around 1.78 times likely to have diabetic retinopathy as those without microalbuminuria. The increase in albuminuria might be the result of vascular damage to the glomerulus, the presence of albuminuria is hypothesized to reflect widespread vascular endothelial dysfunction and increased vascular permeability with vascular leakage of albumin. Many lines of evidence also suggest that increased albuminuria is associated with several other risk factors, including hypertension, arterogenic lipid profiles, inflammation, and a hypercoagulable state, and these factors might accelerate atherosclerosis.

The study also showed a significant deterioration in ACR values after a time interval of two years which shows that out of 106 patients, 62 were normoalbuminuric and 23 of them progressed to microalbuminuria. Of the 40 microalbuminurics 8 reverted to normoalbuminuria and 3 progressed to macroalbuminuria leading to decline of renal status. However the effect of treatment of microalbuminuria if any was not considered as part of this study.

Poor values of HbA1c are known to be associated with increasing incidence of microalbuminuria. In this study only 49 out of 375 patients had a normal HbA1c (< 7.0%). Of the 206 microalbuminuric only 18 (8.7%) had HbA1c<7, the rest 188(91.3%) had HbA1c values more than 7 (p-value <0.001). Several studies have demonstrated this relation between glycemic control and nephropathy.<sup>12</sup> Varghese et al.<sup>9</sup> reported a correlation of the prevalence of microalbuminuria with the fasting blood sugar and with HbA1c levels.

In our study only 11 out of 44 patients who had a normal HbA1c (< 7.0%) manifested microalbuminuria, whereas with HbA1c values more than 7, 27 out of 56 (nearly 50%) had microalbuminuria. It is also interesting to note that when HbA1c rises above 7.0%, 22 out of 27 patients tended to have more than 50mg/l and 7 out of 27 had microalbuminuria touching 300mg/l. Although this is a cross sectional study, these findings raise concern regarding the blatant association between poor glycemic control and microalbuminuria in a rural setting.

Current methods of diabetes management included dietary control in majority of the patients, while 66.4% of the patients were using oral hypo glycemic agents and 33.6% were on combination therapy of insulin and OHA. The highest incidence of microalbuminuria in patients with type 2 diabetes suggests its significant association with cardiovascular and renal events therefore studies examining its natural course preventive and intervention measures are important.<sup>13</sup>

Diabetic kidney disease is under diagnosed and under treated even now, when the early stages of clinical detection is so simple. All the subjects who were contacted by telephone used to monitor only FBS on a monthly or some

patients even admitted to checkup quarterly in a year, as they had the misconception that they are on insulin and that would take care of all complications related to diabetes. The large pool of microalbuminuric group suggest that there could be large increase in overt nephropathy with time, unless aggressive control of diabetes, hypertension is initiated.

The limitation of our study was that ACR was measured at a single point although we recognize the patients with an increased ACR in the first urine sample might not have an increased ACR in the subsequent urine sample.

## Conclusion

This study demonstrated a high prevalence (55.2%) of microalbuminuria in type 2 diabetic patients. Microalbuminuria is significantly associated with presence of diabetic retinopathy, and neuropathy. Given the increasing prevalence of diabetes in India, our findings suggest routine use of urine microalbumin testing to detect nephropathy and administer measures to aggressively prevent the development of micro and macrovascular complications of type 2 diabetes.

**Conflict of Interest:** None.

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