

COMPARATIVE STUDY OF MICROALBUMINURIA AND GLYCATED HEMOGLOBIN LEVELS IN TYPE 2 DIABETIC COMPLICATIONS

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ABSTRACT

Objective: Microalbuminuria occurs when the kidney leaks a small amount of albumin into the urine or when there is an abnormally high permeability for albumin in the renal glomerulus. Microalbuminuria is a powerful risk factor of cardiovascular disease and for the presence and severity of diabetic retinopathy and neuropathy. The aim of this study is to compare the levels of microalbumin and glycated hemoglobin (HbA1c) levels in Type 2 diabetic complications.

Methods: The study includes 100 patients with Type 2 diabetes mellitus visiting the diabetic out-patient department patients with complications, such as hypertension, retinopathy, neuropathy, and cardiovascular complication, was diagnosed based on history and clinical examination and related investigations. Microalbuminuria levels and HbA1c levels are compared in patients with complications (subjects) of Type 2 diabetes mellitus and patients without complications.

Results: The study revealed that microalbumin levels are at a significantly higher range with high HbA1c levels in patients with complications ($p < 0.05$). When compared to patients without complications.

Conclusion: The study supports that strict glycaemic control can prevent microalbuminuria and thereby prevent progress on to diabetic nephropathy in patients with Type 2 diabetes mellitus.

Keywords: Microalbuminuria, Glycated hemoglobin, Diabetic complications

INTRODUCTION

Diabetes mellitus is the most common metabolic disorder characterized by chronic hyperglycemia and disturbances of carbohydrate, fat, and protein metabolism due to absolute or relative deficiency of insulin secretion or action [1]. The risk of chronic complications increases with the duration of hyperglycemia [2]. People with diabetes are at increased risk of chronic complications which affect many organ systems and are responsible for the majority of morbidity associated with the disease.

Chronic complication includes vascular complications microvascular (retinopathy, neuropathy, and nephropathy) macrovascular (coronary artery disease and cerebral vascular disease) [3].

Diabetic retinopathy (DR) is one of the leading causes of blindness in the world [4]. It is one of the most common microvascular complications, affecting 80% of patients over 20 years duration of diabetes [5]. Patients with DR have a higher chance of losing vision about 25 times compared to the normal population. The risk of developing DR or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia [4]. In a clinical-based study, the overall prevalence of DR was 33.4% in Type 2 diabetic patients [6].

Interestingly, another study showed that 7% of Type 2 diabetic patients had DR even at the time of diagnosis of diabetes [7]. The prevalence of DR among the known and newly diagnosed diabetes was 23.1% and 10.9%, respectively. DR is detected clinically by the presence of visible ophthalmoscopic retinal microvascular lesions [8].

A link between renal and retinal angiopathy in diabetes has been long recognized, an effect that may be mediated through an increases in blood pressure, fibrinogen levels, and lipoproteins [9].

Diabetic neuropathy a heterogeneous disease affecting different parts of the nervous system that present with diverse clinical manifestations. They may be focal or diffuse. Most common among the neuropathies are chronic sensorimotor distal symmetric polyneuropathy and the autonomic neuropathies [10]. An internationally agreed simple definition of diabetic peripheral neuropathy for clinical practice is the presence of symptoms and signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes [11].

While a cross-sectional study of 6487 patients found a 28.5% prevalence of neuropathy (young *et al.* 1993), other series reported a range of 5-100%. Using comprehensive evaluation methods, neuropathy was present in 66% of diabetic patients in one series (Dyck *et al.* 1993) 8% have neuropathy at the time of diagnosis of diabetes mellitus, 50% after 25 years. The most common neuropathy was polyneuropathy, with a prevalence of 54% in insulin dependent diabetes mellitus and 45% in non-insulin dependent diabetes mellitus, while focal forms account for 25%. The prevalence increases with the duration of diabetes mellitus [12]. The diagnosis of diabetic peripheral neuropathy can only be made after a careful clinical examination, and all patients with diabetes should be screened annually for diabetic peripheral neuropathy by examining pinprick, temperature and vibration perception (using a 128-HZ tuning fork), 10 g monofilament pressure sensation at the distal halluces, and ankle reflexes. Loss of 10 g monofilament perception and reduced vibration perception predict foot ulcer [13].

Microalbuminuria has become a prognostic marker for cardiovascular disease (CVD), and the presence of microalbuminuria is an indication for the screening of possible vascular disease and aggressive intervention to reduce all cardiovascular risk factors [14,15].

A prevalence of microalbuminuria of 6% was found in a cohort of 1,041 younger patients (aged 18-45 years) with untreated mild hypertension

(140-159/90-99 mmHg) [16]. Hypertension in patients with diabetes is a well-recognized cardiovascular risk factor [17].

Insulin resistance and hyperglycemia combine to make hypertension more prevalent in Type 2 diabetic patients [18]. Approximately 15% of hypertensive patients are diabetic and approximately 75% of Type 2 diabetic patients are hypertensive [19].

When urinary albumin excretion is 30-300 mg/24 hrs or 20-200 µg/min is known as microalbuminuria and referred to as having incipient nephropathy. In India, the prevalence of microalbuminuria varies from 19.7% to 28.5% of unselected Type 2 diabetic patients, whereas the prevalence of diabetic nephropathy in Type 2 diabetic is reported to be 5-9% from various Indian studies [20]. Microalbuminuria was originally established as a predictor of renal failure in patients with diabetes mellitus [21,22]. Glycated hemoglobin (HbA1c) reflects average plasma glucose over the previous 8-12 weeks [23].

It can be performed at any time of the day and does not require any special preparation such as fasting. These properties have made it the preferred test for assessing glycemic control in people with diabetes. More recently there has been substantial interest in using it as a diagnostic test for diabetes and as a screening test for persons at high risk of diabetes [24].

HbA1c could be used as an objective measure of glycemic control. It establishes a validated relationship between A1c and average glucose across a range of diabetes types and patients populations [25].

Diabetic nephropathy patients with Type 2 diabetes has a cumulative prevalence of 30-40% and is currently the leading cause of end-stage renal disease (ESRD) [26,27].

We tried to evaluate the microalbumin and HbA1c levels in various complications and to find out whether there is any association between glycemic control, duration of diabetes, and microalbumin levels.

METHODS

The study was performed after approval from the Institutional Ethics Committee (Ec No: 354/IEC/2012) and informed written consent was obtained from all the participants.

Patient selection

The study was done at SRM Medical College, Hospital and Research Centre and includes 80 patients diagnosed with Type 2 diabetes mellitus and associated complications such as retinopathy, neuropathy, and hypertension as subjects and 20 patients with Type 2 diabetes mellitus as a control. Complications were diagnosed by clinicians based on history, and clinical examination and related investigation were done. Microalbuminuria levels and HbA1c levels were compared in patients with complications (subjects) of Type 2 diabetes mellitus and patients without complications as controls.

Inclusion criteria

Patients who were diagnosed clinically with Type 2 diabetes complications such as retinopathy, neuropathy, and hypertension and whose serum creatinine levels are <1.4 mg/dl.

Exclusion criteria

Patients with serum creatinine more than 1.4 mg/dl and patients with chronic illness, diabetic nephropathy, and pregnancy were excluded from the study.

Sample collection

Fasting blood samples were collected for estimation of blood glucose, creatinine, HbA1c, and lipid profile and urine sample for microalbuminuria of subjects and control.

Biochemical evaluations include fasting plasma glucose, postprandial glucose, HbA1c, lipid profile, serum creatinine, and urine microalbumin were analyzed. Plasma glucose was measured in auto analyzer OLYMPUS AU 400 based on enzymatic method (glucose oxidase and peroxidase) fasting lipid profile - total cholesterol (cholesterol-oxidase), triglyceride (glycerol-oxidase-peroxidase), high-density lipoprotein (enzymatic assay), low-density lipoprotein, very low-density lipoprotein, (Friedewald's calculation Method), and HbA1C (immunoturbidity method) was estimated using commercially available kit on the same day of collection.

The sample obtained for measurement of urine microalbuminuria was stored at -20°C until assessment. Urine microalbuminuria was measured using the standard kit in OLYMPUS AU 400 auto analyzer based on immunoturbidity method, and creatinine by Jaffe's method using commercially available kit.

Statistical analysis

All data were expressed as the mean and standard deviation, the SPSS 20 software was used for the statistical analysis. The statistical significance was analyzed in the subjects and controls using the paired Student's t-test. Significance was considered for all tests ($p < 0.05$). For student t-test significance represented as (*) less significant ($p < 0.05$), (**) significant ($p < 0.01$) and (***) highly significant ($p < 0.001$).

RESULT

In our study, we tried to evaluate the significance of urine microalbuminuria and HbA1c in diabetes with complications and in diabetic patients without any complications who are considered as controls.

In our study, we compared HbA1c in diabetic peripheral neuropathy patients with controls, it was found HbA1c (9.1 ± 2.7) and in controls (5.4 ± 0.7) ($p < 0.00$) urine microalbumin (84.5 ± 72.5) in patients and (15.8 ± 13.9) in controls ($p < 0.000$).

In hypertensive patients HbA1c (7.0 ± 0.7) and in controls (5.4 ± 0.7), with p value ($p < 0.000$) urine microalbumin level was (54.6 ± 28.8) and in controls (15.8 ± 13.9) ($p < 0.000$).

In DR HbA1c (10.4 ± 2.3) and in controls (5.4 ± 0.7) ($p < 0.000$) urine microalbumin levels (113.3 ± 90.1) in patients and (15.8 ± 13.9) in controls with ($p < 0.000$) (Figs. 1-6).

DISCUSSION

Diabetes is a risk factor for various microvascular complications such as retinopathy, neuropathy, cardiovascular disease, and nephropathy. We

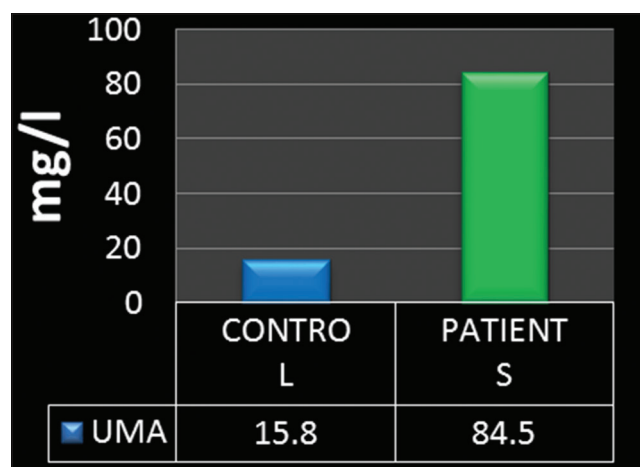


Fig. 1: Mean values of urine microalbuminuria in neuropathy

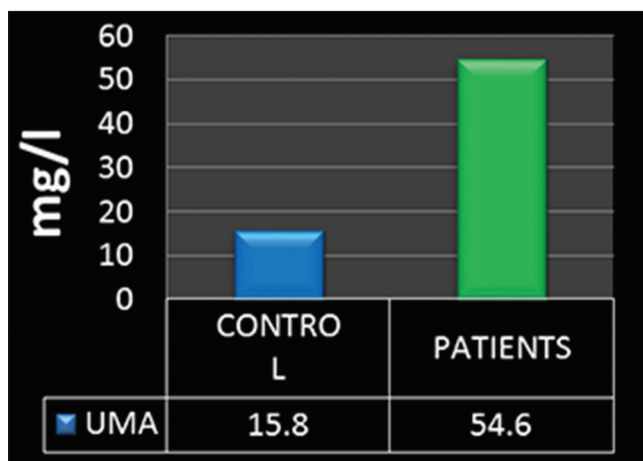


Fig. 2: Mean values of urine microalbuminuria in hypertension

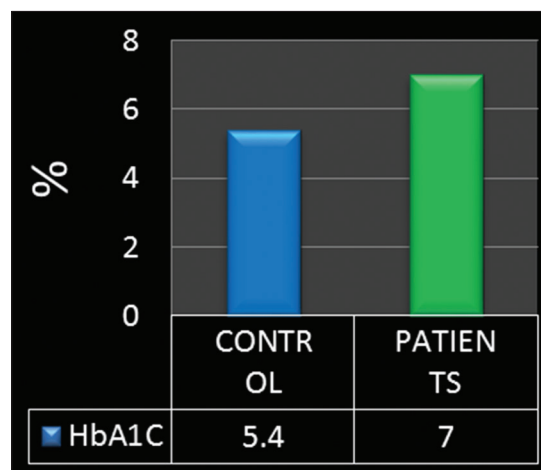


Fig. 5: Mean values of HbA1c in hypertension

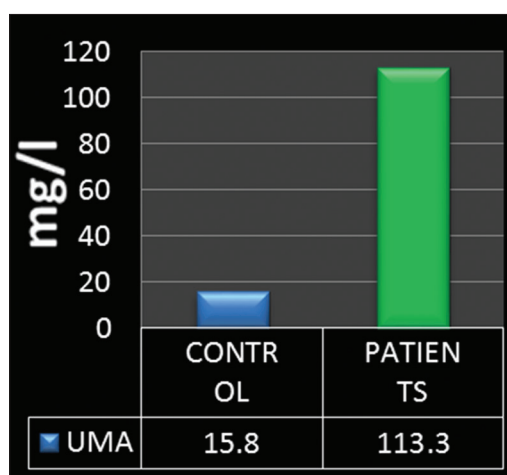


Fig. 3: Mean values of urine microalbuminuria in retinopathy

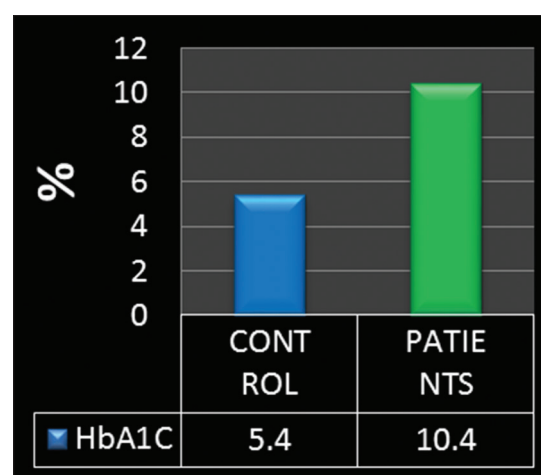


Fig. 6: Mean values of HbA1c in retinopathy

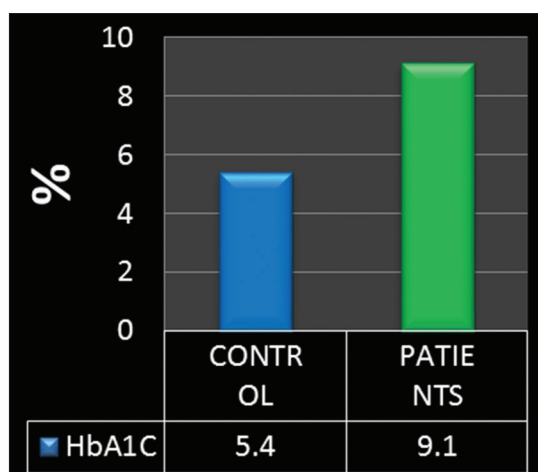


Fig. 4: Mean Values of HbA1c in neuropathy

have conducted a study to evaluate the risk of nephropathy in patients with various diabetes complications such as neuropathy, retinopathy, and hypertension. For this, we have analyzed microalbuminuria and HbA1c levels in all these 3 complications and tried to assess the group which are at earliest risk of nephropathy.

We took 3 groups of patients with 3 different diabetic complications to assess microalbuminuria and HbA1c levels as study groups and diabetes without any complication as a control group.

Our study showed a significant increase in urine microalbumin levels and HbA1c levels in the study group when compared to control group.

The association between microalbuminuria DR, diabetic peripheral neuropathy, and hypertension in the present study could be explained by the view that microalbuminuria might represent a state of generalized vascular dysfunction.

In study group with DR as a complication, microalbuminuria is significantly higher when compared to controls. Studies from North India have suggested a correlation between DR and microalbuminuria [28,29].

Mohan *et al.* reported that the prevalence of DR was significantly higher in Type 2 South Indian diabetic patients with macroproteinuria (35%). Renal involvement only identifies a group of the diabetic patient at higher risk of developing complications. Some studies have reported that duration of diabetes, male sex, and pre-existing retinopathy as major risk factors for microalbuminuria [30].

Some studies have reported that duration of diabetes, male sex, and pre-existing retinopathy as major risk factors for microalbuminuria [31,32].

HbA1c levels in this study group (DR) were also significantly higher ($p < 0.00$) when compared to control.

Gupta *et al.* reported HbA1c to be associated with microalbuminuria; John *et al.* reported poor glycemic control and raised blood pressure as a risk factor of microalbuminuria [28].

In the present study, duration of diabetes and lipid profile was not statically significant when compared with control. Although several studies have reported even through blood pressure levels are elevated when compared to control, significance was not found.

Vijay *et al.* in their studies reported the duration of diabetes, systolic blood pressure, and diastolic blood pressure, the age of patient and serum creatinine to be associated with proteinuria [33].

In diabetic neuropathy study group, our result showed a significance increase in microalbuminuria levels when compared to control groups.

Florakowski *et al.* reported an association of microalbuminuria and neuropathy in the absence of retinopathy and suggested that this provides support for a microalbuminuria element in the pathogenesis of diabetic neuropathy [34].

Paruling *et al.* also reported increased prevalence of peripheral neuropathy in patients with microalbuminuria and non-insulin dependent diabetes mellitus [35].

Young *et al.* reported an association between the advancement of motor, sensory, and autonomic neuropathy that was independent of glycemic control [36].

There was a statically significant increase in HbA1c levels in the study groups (diabetes mellitus with neuropathy) when compared to control.

Significant changes in lipid profile in our study were observed. Statistical significance of low-density lipoprotein and very low-density lipoprotein was observed in the study group when compared to control ($p=0.001$). In our study, we observed microalbuminuria levels were significantly increased in hypertensive patients when compared with controls ($p<0.001$).

The prevalence of microalbuminuria of 6% was found in a cohort study with untreated mild hypertension [16].

After a detailed analysis of all parameters in three groups, we found that there was a significant increase in urine microalbuminuria and HbA1c levels in diabetic complications.

When compared to controls, there was no significant association between HbA1c and Urine microalbuminuria and duration of diabetes, even though it was reported in several studies. Urine microalbuminuria levels are significantly higher in retinopathy cases when compared to neuropathy and hypertension.

Several studies have shown that the amount of microalbuminuria present in a given individual is proportional to the severity of systolic, diastolic, and mean blood pressure, elevation as measured by either a clinical or 24 hrs ambulatory blood pressure monitoring [37,38].

Previous investigators also reported that patients with microalbuminuria had higher blood pressure levels [39].

Individuals with Type 2 diabetes mellitus and hypertension manifest local injury at the level of the glomerular membrane that eventually leads to worsening of generalized vascular leakiness through increased albumin production secondary to renal losses [40,41].

Our study also evaluated the HbA1c levels in the study group and found that there was a statistically significant increase ($p<0.001$) when compared with the control group.

The single most significant determinant that initiates the development of diabetic vasculopathy, as well as nephropathy, is the resultant advanced glycosylation end products and related moieties that are created by hyperglycemia [41-43]. We observed an increase in low-

density lipoprotein and high-density lipoprotein significantly in hypertension patients when compared to controls ($p<0.001$).

CONCLUSION

The presence of microalbuminuria is a powerful predictor of renal and cardiovascular risk in patients with Type 2 diabetes mellitus. Patients with Type 2 diabetes mellitus and associated complications such as retinopathy, neuropathy, and hypertension are at risk of developing diabetic nephropathy. Since Type 2 diabetes mellitus is slow onset disease and most of the Type 2 patients are unaware of the symptoms of diabetes.

Decreasing the levels of albuminuria reduces the risk of adverse renal and cardiovascular complications. Strict glycemic control and blood pressure reduces the albuminuria thereby overt proteinuria. Initiation of drug treatment should be considered in these patients and level of microalbuminuria should be followed. The American Diabetics Association recommends that patients with Type 2 diabetes be tested for albuminuria at the time of initial diabetes diagnosis and yearly thereafter.

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