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Screening of Type 2 Diabetes Mellitus Patients for Micro-albuminuria and Its Relationship with Diabetic Retinopathy

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AKT, OPK, SVM, BDB and VKA were involved in planning and designing of the research protocol. Authors OPK and SVM contributed towards enrolment and screening of patients. Authors PKK, NA, PV and RG were involved in the biochemical investigations and data collection. Author PKK carried out interpretation of data and wrote the first draft of this manuscript. Author AKT, the corresponding author, was involved in overall supervision and critically revised the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The aim of present study was to find out the prevalence of micro-albuminuria and its relationship with diabetic retinopathy in type 2 diabetes mellitus (T2DM) patients.
Study Design: Cross-sectional study.
Place and Duration of Study: Department of Biochemistry and Department of Medicine, University

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College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India, between September 2013 and August 2015.

Methodology: Total 387 clinically diagnosed T2DM patients with age range 30-65 years were enrolled for the study. Morning spot urine samples were collected for analysis of urinary albumin and creatinine on two separate occasions. Serum and urine creatinine were carried out by alkaline picrate Jaffee´s kinetic method. Urine albumin was estimated by turbidometric method by using nephelometer (Nephstar®, Goldsite Diagnostics Inc., USA). On the basis of albumin/creatinine ratio (ACR), patients were classified as normo-albuminuric (albumin/creatinine ratio <30 mg/g creatinine); micro-albuminuric (albumin/creatinine ratio 30-299 mg/g creatinine) and macro-albuminuric (albumin/creatinine ratio ≥300 mg/g creatinine). Patients underwent ophthalmologic examination including fundoscopy for the detection of diabetic retinopathy. Estimated glomerular filtration rate (eGFR) was calculated by Modification of Diet in Renal Disease (MDRD) equation. The plasma glucose, glycosylated hemoglobin, blood urea, serum sodium, serum potassium, total cholesterol, triglyceride and HDL cholesterol etc. investigations were carried out in each patient.

Results: Out of total 387 T2DM patients screened, 159 (41%) were normo-albuminuric, 162 (41.8%) were micro-albuminuric and 66 (17%) were macro-albuminuric. The overall prevalence of micro-albuminuria was 41.8%. The prevalence of micro-albuminuria was 51.2% among males and 48.8% among females. The percentage of patients having micro-albuminuria was found to be increased with increasing duration of diabetes. Micro-albuminuria showed significant correlation with duration of diabetes ($p<0.001$), serum creatinine ($p<0.001$), HbA1c ($p<0.01$) and with eGFR ($p<0.001$). The overall prevalence of diabetic retinopathy in T2DM patients in our study was 29.7% and when the patients were classified according to their albuminuria the prevalence of diabetic retinopathy was found to be 13.8% in normo-albuminuric group, 33.9% in micro-albuminuric group and 57.5% in macro-albuminuric group.

Conclusions: The present study suggests that the onset of micro-albuminuria in T2DM patients is associated with increasing duration of diabetes, poor glycemic control and presence of diabetic retinopathy. Presence of micro-albuminuria in T2DM patients having <5 years of duration of diabetes suggest screening of micro-albuminuria would be beneficial for early detection of DN.

Keywords: Micro-albuminuria; type 2 diabetes mellitus; albumin/creatinine ratio; diabetic retinopathy.

ABBREVIATIONS

T2DM: Type 2 diabetes mellitus; DN: Diabetic nephropathy; ACR: Albumin/creatinine ratio; eGFR: Estimated glomerular filtration rate.

1. INTRODUCTION

Diabetes mellitus (DM) is one of the most common disease characterized by hyperglycemia due to an absolute or relative lack of insulin and/or insulin resistance [1]. DM related morbidity and mortality are associated with vascular complications of diabetes like; retinopathy, nephropathy, neuropathy and cardiovascular diseases which are also considered as burden on the public health worldwide [2].

Diabetic nephropathy (DN) is major micro-vascular complication of DM and is leading cause of end stage renal disease (ESRD). DN is characterized by the excretion of large amounts of urinary proteins, commonly albumin and decrease in estimated glomerular filtration rate (eGFR). Presence of micro-albumin in urine (micro-albuminuria) is hallmark of diabetic nephropathy [1,3]. The persistent leakage of these proteins into urine results in overt diabetic nephropathy, which further results in the development of ESRD [4]. In India, various studies have reported marked variation in the prevalence of micro-albuminuria. Gupta et al. [5] reported 26.6% micro-albuminuria among 65 T2DM non-proteinuric patients of north India while, John et al. [6] and Chowta et al. [7] reported the prevalence of micro-albuminuria to be 19.7% and 37%, respectively in T2DM patients of South India.

Diabetic retinopathy (DR) is also a micro-vascular complication of diabetes mellitus. It is characterized by retinal micro-vasculature, leading to retinal hypoperfusion, increased vascular permeability and intraocular proliferation of retinal vessels [8]. Fundus examination is

performed for the detection of diabetic retinopathy [9]. Various studies have reported 16% to 53.4% prevalence of diabetic retinopathy in T2DM patients [10,11,12,13].

A relationship of micro-albuminuria and diabetic retinopathy in patients with type 1 diabetes have also been reported in various studies [14,15] however, there is paucity of data regarding the association of micro-albuminuria with diabetic retinopathy in type 2 diabetes mellitus [16,17]. Duration of diabetes, poor glycemic control, high blood pressure and age etc. are also found to be associated with the micro-vascular complications of T2DM [8,18]. Early screening of various risk factors associated with development of vascular complications is essential to reduce the socioeconomic burden of diabetes on public health. Therefore, the present study was carried out to screen type 2 diabetes mellitus patients for the presence of micro-albuminuria and diabetic retinopathy and also to find out its relationship.

2. MATERIALS AND METHODS

2.1 Study Design

This cross-sectional study was carried out on clinically diagnosed type 2 diabetic patients who attended Diabetic clinic, Department of Medicine at University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India, between September 2013 and August 2015. All T2DM patients (n = 387) who attended the diabetic outpatient clinic during the above mentioned period were screened for urinalysis. Urinalysis was done in a random spot urine sample by using dipstick and subsequently, the urine samples were analysed for quantitative albumin estimation by nephelometer. During the enrolment, information regarding personal data (age, sex, family history, duration of diabetes/hypertension etc.) and any previous laboratory/ophthalmologic examination were recorded. Detailed assessment was carried out to exclude other possible causes of micro-albuminuria. The patient's blood pressure was measured after five minutes of rest in seating position by a mercury sphygmomanometer. Blood pressure ≥140/90 mmHg was considered as hypertensive. The study was approved by Institutional Ethics Committee-Human Research (IEC-HR) of University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi and written informed consent was obtained from all the enrolled patient.

2.2 Routine Biochemical Parameters Analysis

The plasma glucose was analysed by glucose oxidase peroxidase (GOP-POD) method, glycosylated hemoglobin was estimated by cation-exchange resin method, total cholesterol was estimated by cholesterol oxidase/peroxidase method, triglycerides was estimated by enzymatic colorimetric method and HDL cholesterol was estimated by phosphotugstate/ magnesium precipitation method.

2.3 Estimation of Urinary Albumin/ Creatinine Ratio (ACR) and Glomerular Filtration Rate (GFR)

Serum and urine creatinine were carried out by alkaline picrate Jaffee´s kinetic method [19]. Morning spot urine samples were collected for urine albumin and urine creatinine test. Urine albumin was estimated by turbidometric method by using nephelometer (Nephstar®, Goldsite Diagnostics Inc., USA). The sensitivity limit is 10 mg/L. Albumin /creatinine ratio was expressed in mg/g creatinine. On the basis of albumin/creatinine ratio (ACR), patients were classified in three groups: normo-albuminuric (albumin/creatinine ratio <30 mg/g creatinine); micro-albuminuric (albumin/creatinine ratio 30-299 mg/g creatinine) and macro-albuminuric (albumin/creatinine ratio ≥300 mg/g creatinine). Estimated glomerular filtration rate was calculated by Modification of Diet in Renal Disease (MDRD) equation [20].

2.4 Ophthalmologic Examination for Diabetic Retinopathy

Fundoscopic examination was done for the detection of diabetic retinopathy and patients were categorized according to the stages of retinopathy; no diabetic retinopathy (NO DR), mild non-proliferative diabetic retinopathy (mild NPDR), moderate non-proliferative diabetic retinopathy (moderate NPDR), severe non-proliferative diabetic retinopathy (severe NPDR) and proliferative diabetic retinopathy (PDR).

2.5 Statistical Analysis

All statistical analysis were done by SPSS version 20.0. Data was expressed as mean±SD. Student's t- test was used for comparison of clinical and biochemical variables of normo-albuminuric group to micro- and macro-

albuminuric group. Pearson's correlation analysis was carried out to find association of micro-albuminuria with duration of diabetes, serum creatinine, HbA1c and with eGFR. *P*<0.05 was considered as statistically significance level.

3. RESULTS

3.1 Clinical and Biochemical Characteristics of the Normo-albuminuric, Micro-albuminuric and Macro-albuminuric Subjects

The clinical and biochemical characteristics of the normo-albuminuric, micro-albuminuric and macro-albuminuric patients are listed in Table 1. Urinalysis revealed 159 (41%) T2DM patients as normo-albuminuric, 162 (41.8%) of the patients as micro-albuminuric and 66 (17.0%) as macro-albuminuric. The prevalence of micro-albuminuria among males was found to be 51.2% and among females, it was 48.8%. In this study, 187 (48.3%) were females and 200 (51.7%) were males. Out of 387 patients, forty three (11.1%) patients had family history of diabetes. Sixty five (16.7%) had family history of hypertension and eight (2%) had family history of renal disease. In micro-albuminuric patients, mean age was 48.96 ± 8.3 years and the mean of duration of diabetes was 8.8 ± 3.7 years found to be statistically significant as compared with normo-albuminuric patients. In this group 61 (37.7%) patients had hypertension with significantly increased systolic and diastolic blood pressure as compared to normo-albuminuric patients. HbA1c, serum creatinine, blood urea, eGFR, sodium and potassium levels were also found to be significantly higher in micro-albuminuric patients when compared with the normo-albuminuric patients. However, fasting plasma glucose, post prandial plasma glucose, hemoglobin, serum total cholesterol, high density lipoprotein and triglyceride levels were not found statistically significant when micro-albuminuric patients compared with normo-albuminuric patients.

Table 1. Clinical and biochemical characteristics of the study subjects

Parameters	Normo-albuminuria (n = 159)	Micro-albuminuria (n = 162)	Macro-albuminuria (n = 66)
Male /Female (n)	85/74	83/79	32/34
Family history of diabetes (n)	10	15	18
Family history of hypertension (n)	8	20	37
Family history of renal disease (n)	1	4	3
Hypertension [n (%)]	51 (32%)	61 (37.7%)	44 (66.67%)
Age (years)	48.86 ± 8.4	48.96 ± 8.3	49.01 ± 8.8
Duration of diabetes (years)	6.4 ± 3.9	8.8 ± 3.7[a]	9.7 ± 3.8[b]
Duration of hypertension (years)	2.9 ± 1.1	3.1 ± 1.3[a]	3.3 ± 1.2[d]
SBP (mmHg)	138 ± 11.5	146 ± 19.3[a]	149 ± 20.1[b]
DBP (mmHg)	80.5 ± 11.12	84.03 ± 10.9 [c]	84.8 ± 11.24 [d]
Fasting plasma glucose (mg/dL)	150 ± 55.6	157 ± 54.5	158 ± 54.2
Post prandial plasma glucose (mg/dL)	232 ± 80.87	238 ± 73.65	237 ±70.40
HbA1c (%)	6.6 ± 2.0	8.3 ± 2.5[a]	8.6 ± 2.3[b]
Serum creatinine (mg/dL)	0.92 ± 0.35	0.96 ± 0.30 [c]	1.16 ± 0.58[b]
Blood urea (mg/dL)	30.8 ± 19.4	35 ± 17.8[c]	41.8 ± 21.6[b]
Serum sodium (mEq/L)	137 ± 2.4	139 ± 5.3[a]	140 ± 3.9[b]
Serum potassium (mEq/L)	4.2 ± 0.68	5.0 ± 0.74[a]	5.2 ± 0.73[b]
eGFR (ml/minute/1.73m^2)	89.5 ± 20.7	80.8 ± 25.6[a]	65.7 ± 25.3[b]
Hemoglobin (g/dL)	11.7 ± 2.3	10.2 ± 1.8	11.4 ± 2.0
Serum total cholesterol (mg/dL)	193 ± 52	194 ± 51	206 ± 48.4
Serum HDL (mg/dL)	36.0 ± 7.07	35 ± 7.12	36.9 ± 7.71
Serum LDL (mg/dL)	112 ± 38.6	120 ± 60	119 ± 42
Serum triglyceride (mg/dL)	139 ± 99	148 ± 68	160 ± 63

Data are expressed as number (n), percentage (%) or mean ± SD, P<0.05; level of significance, a: P<0.0001 vs. micro-albuminuria, b: P<0.0001 vs. macro-albuminuria, c: P<0.01 vs. micro-albuminuria, d: P<0.01 vs. macro-albuminuria, Diastolic blood pressure; DBP, Systolic blood pressure; SBP

3.2 Correlation of Micro-albuminuria with Duration of Diabetes, Serum Creatinine, HbA1c and eGFR

Correlation of micro-albuminuria with duration of diabetes, serum creatinine, HbA1c and eGFR are presented in Table 2. A significant correlation was observed with duration of diabetes (*P*<0.001), serum creatinine (*P*<0.001), HbA1c (*P* <0.01) and with eGFR (*P*<0.001).

3.3 The Status of Micro-albuminuria with Increasing Duration of Diabetes

The micro-albuminuria in relation to increasing duration of diabetes is shown in Table 3. In patients with duration of diabetes ≤5 years, the prevalence of micro-albuminuria was 37.6%. When the duration of diabetes was 6 - 10 years, 11 - 15 years, 16 - 20 years and > 20 years the prevalence was found to be 41.1%, 43.1%, 57.14% and 66.6%, respectively.

3.4 Prevalence of Diabetic Retinopathy and Its Relationship with Albuminuria

Prevalence of diabetic retinopathy and its relationship with albuminuria is listed in Table 4. The overall prevalence of diabetic retinopathy was 29.7% in T2DM patients. Diabetic retinopathy was observed 13.8% in normo-albuminuric group, 33.9% in micro-albuminuric group and 57.5% in macro-albuminuric group of T2DM patients. When patients were categorized based on the degree of retinopathy, 3.6% patients had PDR and 25.9% had NPDR. Among patients with NPDR, 13.1% had mild NPDR, 5.9% had moderate NPDR and 6.9% had severe NPDR [Table 4A]. Taking T2DM with normo-albuminuria as the reference, the odds ratios for association of diabetic retinopathy with albuminuria were calculated. Micro-/macro-albuminuria showed statistically significant association with diabetic retinopathy [Table 4B].

Table 2. Correlation of micro-albuminuria with duration of diabetes, HbA1c, serum creatinine and eGFR

(n =162)	Duration of diabetes	Serum creatinine	HbA1c	eGFR
	r = 0.396	r = 0.395	r = 0.200	r = - 0.251
	P<0.001	*P*<0.001	*P*<0.01	*P*<0.001

r = Pearson's correlation coefficient, P<0.05; level of significance

Table 3. M**icro-albuminuria in relation with duration of diabetes**

Duration of diabetes (years)	Total subjects (n)	Prevalence (%)
≤5	77	29 (37.6)
6 -10	124	51 (41.1)
11-15	176	76 (43.1)
16 - 20	07	04 (57.14)
>20	03	02 (66.6)

Data are expressed as number (n) and percentage (%)

Table 4A. Prevalence of diabetic retinopathy

Albuminuria	Diabetic retinopathy					Total (n = 387)
	NO DR	PDR	Mild NPDR	Moderate NPDR	Sever NPDR	
Normo-albuminuria (n = 159)	137 (86.2%)	02 (1.3%)	10 (6.3%)	05 (3.1%)	05 (3.1%)	159 (100%)
Micro-albuminuria (n = 162)	107 (66.1%)	8 (4.9%)	25 (15.4%)	10 (6.2%)	12 (7.4%)	162 (100%)
Macro-albuminuria (n = 66)	28 (42.5%)	04 (6.0%)	16 (24.2%)	08 (12.1%)	10 (15.2%)	66 (100%)
Total (n = 387)	272 (70.2%)	14 (3.6%)	51 (13.1%)	23 (5.9%)	27 (6.9%)	387 (100%)

Data are expressed as number and percentage (%), DR; diabetic retinopathy, PDR; proliferative diabetic retinopathy, NPDR; non-proliferative diabetic retinopathy

Table 4B. Association between albuminuria and diabetic retinopathy

	NO DR	DR (all degrees of retinopathy)	OR (CI 95%)	P value
Normo-albuminuria (n = 159)	137	22	1	
Micro-albuminuria (n = 162)	107	55	3.2 (1.86-5.49)	0.0001
Macro-albuminuria (n = 66)	28	38	8.45 (4.35-16.41)	0.0001

Data are expressed as number (n), OR; Odds ratio, CI; Confidence interval, DR; diabetic retinopathy, NO DR; No diabetic retinopathy; P<0.05; level of significance

4. DISCUSSION

Vascular complications associated with diabetes mellitus has become a major health issue worldwide. Diabetic nephropathy and diabetic retinopathy are major micro-vascular complications among them. Micro-albuminuria is an early stage marker for detection and progression of diabetic nephropathy [21]. In the present study, overall prevalence of micro-albuminuria and macro-albuminuria was found to be 41.8% and 17.0%, respectively in among T2DM patients screened. The prevalence of micro-albuminuria in patients with type 2 diabetes in different parts of India is about 20-37% [6,7,22,23]. The variation in prevalence of micro-albuminuria is mainly due to differences in duration of diabetes and the test used for detection of micro-albuminuria as test strips are less sensitive as compared to nephelometer assay.

We observed, significant (*P*<0.001) correlation of micro-albuminuria with duration of diabetes indicating that the prevalence of micro-albuminuria increased with increasing duration of diabetes Our result is consistent with the findings of several studies [24,25,26,27], which state that the duration of diabetes has significant contribution for the development of micro-albuminuria. Significant (*P*<0.01) correlation was also observed between micro-albuminuria and HbA1c. The increased HbA1c levels found in our study indicates that our subjects are under poor glycemic control. The association of poor glycemic control with micro-albuminuria has been well established by previous reports [5,28,29, 30]. On the contrary, "Micro-albuminuria Collaborative Study Group" of United Kingdom [31] has reported that progression to clinical albuminuria is not associated with the HbA1c. We also observed significant correlation of serum creatinine (*P*<0.001), and eGFR (*P*<0.001) with micro-albuminuria showing its association with decline in renal function. It has been reported earlier that progression of micro-albuminuric patients to abnormal plasma creatinine level takes place in about 2 to 3% patients [22]. At an early stage micro-albuminuric patients does not show significant correlation of micro-albuminuria with serum creatinine and creatinine clearance [7].

The overall prevalence of diabetic retinopathy in T2DM patients in our study was 29.7% and when the patients were classified according to stage of albuminuria, the prevalence of diabetic retinopathy was found to be 13.8% in normo-albuminuric group, 33.9% in micro-albuminuric group and 57.5% in macro-albuminuric group. It shows that number of patients with diabetic retinopathy increases progressively with the stage of albuminuria. Numerous studies have shown 16 to 53.4% prevalence of DR in T2DM patients [10,11,12,13]. These studies have also shown significant relationship between the degree of diabetic retinopathy and stages of albuminuria similar to our finding. We also observed that T2DM patients had diabetic retinopathy without micro-/macro-albuminuria at early stage or vice-versa. This finding has been supported by various studies that report 10-30% prevalence of DR in T2DM patients with normo-albuminuria [10,32,33,34]. Out of 387 patients, 228 were having albuminuria (Table 4B), and of these, 40.7% were having both DR and albuminuria while, 59.3% were having albuminuria in absence of DR, suggesting that albuminuria in DR-free T2DM patients may be the consequence of non-diabetic renal diseases (NDRD). However, in general it is likely that NDRD patients having increased duration of DM (>10 years) likely to have DN while, patients with shorter duration of DM may have NDRD. Prakash et al. [35], reported that longer duration of diabetes (>10 years) is strongest predictor of

DN and patients having NDRD alone had shorter duration of DM. They have also mentioned that absence of DR favour NDRD but does not exclude occurrence of DN.

We observed that in addition to diabetic retinopathy, HbA1c and duration of diabetes were also the major risk factors for micro-albuminuria in T2DM patients. Similar to our observation, many studies have reported high blood pressure, poor glycemic control, age, longer duration of diabetes and serum creatinine level as risk factors for micro-albuminuria [8,18,36,37].

5. STRENGTH AND LIMITATIONS OF STUDY

We used dipstick (qualitative) as well as urinary albumin/creatinine ratio method (quantitative) to detect albuminuria in T2DM patients in spot urine samples at 2 separate occasions. The use of both qualitative and quantitative method for detection of albuminuria makes our data more reliable for screening. This is a hospital-based study, therefore, it is not representative and extrapolation to overall population may not provide a correct picture. Also distribution of patients with regard to duration of diabetes is not uniform [Table 3], which may have affected the overall prevalence data of microalbuminuria.

6. CONCLUSION

Onset of micro-albuminuria in T2DM patients is associated with duration of diabetes, glycemic control and presence of diabetic retinopathy. Screening of micro-albuminuria should be carried out in all T2DM patients to facilitate an early and quick identification of DN/NDRD to arrest its further progression.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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