

Early screening of type 2 diabetes mellitus patients for micro-albuminuria and its relationship with diabetic retinopathy

ABSTRACT

Aims: The aim of present study was to find out the prevalence of micro-albuminuria and their inter-relationship with diabetic retinopathy in type 2 diabetes mellitus (T2DM) patients as early screening for the prevention of micro-vascular complications.

Study design: Cross-sectional study

Place and Duration of study: Department of Biochemistry and Department of Medicine, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India, between September 2013 and April 2015.

Methodology: Total (n = 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.). 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, hemoglobin, total cholesterol, triglyceride and HDL cholesterol etc. investigations were carried out at hospital laboratory services, G.T.B. Hospital.

Results: After screening, out of 387 patients, 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 micro-albuminuria was found to be increased with increasing duration of diabetes. Micro-albuminuria also showed a significant correlation with duration of diabetes (p<0.001), serum creatinine (p<0.01), HbA1c (p<0.05) and with eGFR (p<0.05). In the present study, the overall prevalence of diabetic retinopathy was 29.7% among T2DM patients 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 early onset of micro-albuminuria in the North Indian T2DM patients is associated with increasing duration of diabetes, poor glycemic control and presence of diabetic retinopathy. Early screening for micro-albuminuria in both newly and already diagnose patients would be beneficial to reduce the micro-vascular complications among T2DM patients. The study also reveals a relationship between the diabetic retinopathy with the progression of albuminuria in T2DM patients.

Keywords: Micro-albuminuria, Type 2 diabetes mellitus, Albumin/creatinine ratio, Diabetic retinopathy

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. Presence of micro-albumin in urine (micro-albuminuria) is the early indication of diabetic nephropathy [1, 3]. The persistent leakage of these proteins into urine results in overt diabetic nephropathy, which further results in the gradual development of ESRD [4]. In India,

various studies have reported marked variation in the prevalence of micro-albuminuria. Gupta et al, reported a prevalence of micro-albuminuria is 26.6% of 65 T2DM non-proteinuric patients of north India [5] while, John et al and Chowta et al, reported the prevalence of micro-albuminuria in south India are 19.7% and 37%, respectively [6, 7].

Diabetic retinopathy (DR) is also a micro-vascular complication of diabetes mellitus. It is characterized by progression in 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].

Micro-albuminuria and diabetic retinopathy relationship 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, metabolic syndrome, poor glycemic control, high blood pressure and old age etc. were also found to be associated with the micro-vascular complications of T2DM [8,18]. Early screening for micro-albuminuria, diabetic retinopathy and identifying the various risk factors associated with vascular complications are required to reduce the socioeconomic burden of diabetes on public health. Therefore, the present study was carried out for early screening of type 2 diabetes mellitus patients for the presence of micro-albuminuria and diabetic retinopathy and also to find out their interrelationship.

2. MATERIAL AND METHODS

2.1. Study design

This cross-sectional study was carried out on clinically diagnosed type 2 diabetic patients who were attending 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 (n = 387) patients attending the diabetic outpatient clinic were screened for urinalysis. Urinalysis was done in a random spot urine sample by using dipsticks. After positive dipsticks the urine samples were then analysed for quantitative protein estimation by nephelometer. During the enrollment, preliminary questionnaires that included personal data, the patient's ophthalmologic examination and laboratory investigations were also done. Detailed assessment was carried out to exclude other possible causes of micro-albuminuria. The patient's blood pressure was measured by mercury sphygmomanometer. Five minutes after resting in the sitting position blood pressure $\geq 140/90$ mmHg was considered as hypertensive.

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 phosphotungstate/magnesium precipitation method. These investigations were carried out at hospital laboratory services, G.T.B. Hospital.

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.). 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 $\pm$ 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 applied to observe 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. On urinalysis in all subjects, 159 (41%) were normo-albuminuric, 162 (41.8%) of the patients were micro-albuminuric and 66 (17.0%) were 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. Forty three (11.1%) patients had a 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 stastically 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. Fasting blood glucose, post prandial blood glucose, HbA1c, serum creatinine and blood urea levels were also found to be significantly higher in micro-albuminuric patients when compared with the normo-albuminuric patients. However, serum total cholesterol, high density lipoprotein and triglyceride levels were not found statistically significant when normo-albuminuric patients were compared with micro-albuminuric and macro-abuminuric 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
DBP (mmHg)	80.5 ± 11.12	84.03 ± 10.9^a	84.8 ± 11.24^b
Fasting blood glucose (mg/dL)	150 ± 55.6	157 ± 54.5^a	158 ± 54.2^b
Post prandial blood glucose (mg/dL)	232 ± 80.87	238 ± 73.65^a	237 ± 70.40^b
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^a	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^a	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 $\pm$ 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 ($P<0.01$), HbA1c ($P<0.05$) and with eGFR ($P<0.05$).

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

(n =162)	Duration of diabetes	Serum creatinine	HbA1c	eGFR
	$r = 0.396$ $P<0.001$	$r = 0.395$ $P<0.01$	$r = 0.200$ $P<0.05$	$r = - 0.251$ $P<0.05$

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

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.

Table 3. Micro-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 (%)

3.4. Prevalence of diabetic retinopathy and its relationship with albuminuria

Prevalence of retinopathy and its relationship with albuminuria is listed in Table 4. The overall prevalence of retinopathy was 29.7%. In normo-albuminuric group 13.8%, in micro-albuminuric group 33.9% and in macro-albuminuric group 57.5% patients had diabetic retinopathy. When patients were categorized based on the degree of retinopathy, 3.6% patients were found to have PDR and 25.9% have NPDR. Among patients with NPDR, 13.1% had mild NPDR, 5.9% had moderate NPDR and 6.9% had severe NPDR.

Table 4. Relationship between albuminuria and 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

4. DISCUSSION

Diabetes mellitus associated with vascular complications has become a major health issue in India. Diabetic nephropathy and diabetic retinopathy are major micro-vascular complications among them. The present study was conducted on type 2 diabetic patients of North Indian population, Delhi, India. In the present study, overall prevalence of micro-albuminuria and macro-albuminuria were found to be 41.8% and 17.0%, respectively. However, the prevalence of micro-albuminuria in patients with type 2 diabetes in different parts of India is about 30- 49%, which is similar to our results [21]. In contrast to our finding, Ghai et al. found that the prevalence of micro-albuminuria was 25% [22]. Micro-albuminuria is an early stage marker for detection and progression of DN [23]. Therefore, the variation in prevalence of micro-albuminuria may be due to differences in population, sample collection methods, calculation and ethnicity.

In the present study, micro-albuminuria showed highly significant correlation with duration of diabetes ($P<0.001$). We also found the prevalence of micro-albuminuria was increased with increasing duration of diabetes. It indicates that the long term diabetes may lead to progression of diabetic nephropathy. Our results were consistent with the findings of several studies [24, 25, 26, 27], which showed duration of diabetes has significant contribution for the development of micro-albuminuria. Significant correlation was also observed in micro-albuminuria and HbA1c ($P<0.05$). The increased HbA1c levels found in our study indicates that our subjects were 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] reported that progression to clinical albuminuria was not associated with the HbA1c. We also observed significant correlation of micro-albuminuria with serum creatinine ($P<0.01$), and eGFR ($P<0.05$) which indicates its association with decline in renal function. In contrast to our results, Chowta et al, found insignificant correlation of micro-albuminuria with serum creatinine and creatinine clearance and also reported that micro-albuminuria is warning signal, if ignored [7].

In this study, the overall prevalence of diabetic retinopathy was 29.7% and when the patients were classified according to their albuminuria stage, 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 patient with diabetic retinopathy increases progressively with the stage of albuminuria. Numerous studies were carried out to determine the prevalence of diabetic retinopathy in type 2 diabetes, which showed different prevalence range of 16 to 53.4% [10, 11, 12, 13]. These studies also showed a relationship between the degree of diabetic retinopathy and stages of albuminuria. Our results also revealed that patients with T2DM may have diabetic retinopathy without micro-/macro-albuminuria at early stage or vice-versa. This finding has been supported by various studies that reported 10-30% prevalence of DR in T2DM patients with normo-albuminuria [10, 32, 33, 34]. It indicates that micro-albuminuria is not a good predictor for DR but diabetic retinopathy is associated with progression of albuminuria.

Our study showed that in addition to diabetic retinopathy, HbA1c and duration of diabetes are also the major risk factors for micro-albuminuria in north Indian T2DM patients. In support to our study, some studies have reported the duration of the diabetes and diabetic retinopathy as major risk factors for micro-albuminuria [35, 36]. High blood pressure, poor glycemic control, old age, longer duration of diabetes and serum creatinine are also the risk factors reported in many studies [8, 18]. Screening of micro-albuminuria directs need of better control of blood glucose and identification of associated risk factors to prevent the development and progression of micro-vascular complications in T2DM.

5. STRENGTH AND LIMITATIONS OF STUDY

In our study urinary albumin/creatinine ratio method was also used along with dipstick method to detect the albuminuria in T2DM patients in spot urine samples at 2 separate occasions. Therefore, this study could provide a reliable data of T2DM patients at an early stage.

Since, this was a hospital-based study, therefore, it may not be representative and applicable to overall population of North India. The study included small number of subjects. A large sample size and multicentre study would be needed in the future.

6. CONCLUSION

Being a developing country; there is a dire need that micro-albuminuria should be carried out in both, newly diagnosed as well as already diagnosed T2DM patients to facilitate an early and quick identification of diabetic nephropathy. Good glycemic control and a healthy lifestyle are especially important for diabetic patients and for those with a family history of diabetes.

CONSENT

All authors declare that written informed consent was obtained from the patient.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

LIST OF ABBREVIATIONS

T2DM, type 2 diabetes mellitus; DN, diabetic nephropathy; ACR, albumin/creatinine ratio, estimated glomerular filtration rate; eGFR

REFERENCES

1. Powers A C. Diabetes Mellitus. In: Jameson JL. (Editor) Harrison's Endocrinology. 1st ed New York: McGraw-Hill; 2006, p 303–4.
2. Bonadonna RC, Cucinotta D, Fedele D, Riccardi G, Tiengo A. Metascreen Writing Committee. The metabolic syndrome is a risk indicator of microvascular and macrovascular complications in diabetes: Results from Meta screen, a multicenter diabetes clinic based survey. *Diabetes Care*. 2006; 29:2701-7.
3. Microalbuminuria test. Available at [www.nlm.nih.gov/ Medline plus/ency/article/003591.htm](http://www.nlm.nih.gov/Medline_plus/ency/article/003591.htm) [Accessed Oct 19, 2008].
4. Vergouwe Y, Soedamah-Muthu SS, Zgibor J, Chaturvedi N, Forsblom C, Snell-Bergeon JK, et al. Progression to microalbuminuria in type 1 diabetes: development and validation of a prediction rule. *Diabetologia*. 2010; 53:254-62.
5. Gupta DK, Verma LK, Khosla PK, et al. The prevalence of microalbuminuria in diabetes: a study from north India. *Diabetes Res Clin Pract*. 1991; 12:125–8.
6. Diabetic nephropathy in non-insulin dependent diabetes. *Indian J Med Res*. 1991; 94:24–9.
7. Chowta NK, Pant P, Chowta MN. Microalbuminuria in diabetes mellitus: Association with age, sex, weight, and creatinine clearance. *Indian J Nephrol*. 2009; 19: 53-56.
8. Kumar HKVS, Kota SK, Basile A, Modi KD. Profile of microvascular disease in type 2 diabetes in a tertiary health care hospital in India. *Ann Med Health Sci Res*. 2012; 2: 103–08. DOI: 10.4103/2141-9248.105654, PMID: PMC3573501.
9. Sobngwi E, Mbanya JC, Moukouri EN, Ngu KB. Microalbuminuria and retinopathy in a diabetic population of Cameroon. *Diabetes Res Clin Pract*. 1999; 44:191-96.
10. Masoud R Manaviat MR, Afkhami M, Shoja MR. Retinopathy and microalbuminuria in type II diabetic patients. *BMC Ophthalmology*. 2004; 4:9. DOI: 10.1186/1471-2415-4-9

- 287 11. Liu DP, Molyneaux L, Chua E, Wang YZ, Wu CR, Jing H, et al. Retinopathy in a Chinese
288 population with type 2 diabetes: factors affecting the presence of this complication at diagnosis of
289 diabetes. *Diabetes Res Clin Pract.* 2002; 56:125-31.
- 290 12. Wirta O, Pasternack A, Mustonen J, Laippala P, Lahde Y. Retinopathy is independently related to
291 microalbuminuria in type 2 diabetes mellitus. *Clin Nephrol.* 1999; 51:329-34.
- 292 13. Erasmus RT, Oyeyinka G, Arije A. Microalbuminuria in non-insulin- dependent (type 2) Nigerian
293 diabetics: relation to glycaemic control, blood pressure and retinopathy. *Postgrad Med J.* 1992;
294 68:638-42.
- 295 14. Lovestam-Adrian M, Agardh E, Agardh CD. The temporal development of retinopathy and
296 nephropathy in type 1 diabetes mellitus during 15 years diabetes duration. *Diabetes Res Clin Pract.*
297 1999; 45:15-23.
- 298 15. Marshall SM, Alberti KG. Comparison of the prevalence and associated features of abnormal
299 albumin excretion in insulin-dependent and noninsulin-dependent diabetes. *Q J Med.* 1989; 70:61-71.
- 300 16. Savage S, Estacio RO, Jeffers B, Schrier RW. Urinary albumin excretion as a predictor of diabetic
301 retinopathy, neuropathy, and cardiovascular disease in NIDDM. *Diabetes Care.* 1996; 19:1243-48.
- 302 17. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR, UKPDS Study Group. Risk factors for
303 renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. *Diabetes.* 2006; 55:1832-
304 39.
- 305 18. Foucan L, Deloumeaux J, Donnet JP, Bangou J, Larifla L, Messerschmitt C, et al. Metabolic
306 syndrome components in Indian migrants with type 2 diabetes. A matched comparative
307 study. *Diabetes Metab.* 2006; 32:337-42.
- 308 19. Bowers LD, Wong ET. Kinetic serum creatinine assays. II. A critical evaluation and review. *Clin*
309 *Chem.* 1980; 26: 555-61.
- 310 20. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, et al. Using standardized serum creatinine
311 values in the modification of diet in renal disease study equation for estimating glomerular filtration
312 rate. *Ann Intern Med.* 2006; 145:247-54.
- 313 21. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. UKPDS GROUP.
314 Development and progression of nephropathy in type 2 diabetes: The United Kingdom prospective
315 diabetes study. *Kidney Int.* 2003; 63:225-32.
- 316 22. Ghai R, Verma ND, Goel A, Bhatnagar MK, Kapoor P, Vashishta A. Microalbuminuria in non-
317 insulin dependent diabetes and essential hypertension: A marker of severe disease. *J Assoc*
318 *Physicians India.* 1994; 42:771-74.
- 319 23. Maahs DM, Snively BM, Bell RA, Dolan L, Hirsch I, Imperatore G, et al. Higher Prevalence of
320 Elevated Albumin Excretion in Youth with Type 2 than Type 1 Diabetes: The SEARCH for Diabetes in
321 Youth Study. *Diabetes Care.* 2007; 30:2593–8.
- 322 24. Vishwanathan V, Snehalatha C, Shina K, Ramachandran A. Persistent microalbuminuria in type 1
323 diabetic subjects in South India. *J Assoc Physicians India.* 2002; 50: 1259-61.
- 324 25. Moayeri H, Dalili H. Prevalence of microalbuminuria in Children and Adolescents with Diabetes
325 Mellitus Type 1. *Acta Medica Iranica.* 2006; 44: 105-10.

- 326 26. Andrzej S. Krolewski et al. The changing natural history of nephropathy in type 1 Diabetes. Am J
327 of Med.1985; 78:785-94.
- 328 27. Kofoed-Enevoldsen A. et al. Declining incidence of persistent proteinuria in Type 1 (insulin
329 dependent) diabetic patients in Denmark. Diabetes. 1987; 36:205-09.
- 330 28. Diabetes Control and Complications Trial (DCCT) Research Group. The effect of intensive
331 treatment of diabetes on the development and progression of long-term complications in Insulin
332 Dependent Diabetes Mellitus. Engl. Med. 1993; 329-977.
- 333 29. Gupta R, Kawatra A, Gehlot S, Agrawal RP, Binawara BK, Sharma H. Microalbuminuria and its
334 association with risk factors among type 1 diabetes mellitus patients attending a tertiary care hospital :
335 A cross sectional study. International J. of Healthcare & Biomedical Research. 2013; 3: 109-19.
- 336 30. Mulec H, Blohme G. et al. The effect of metabolic control on rate of decline in renal function in
337 IDDM with overt diabetic nephropathy. Nephrol Dial Transplant. 1998; 13: 651-55.
- 338 31. Microalbuminuria Collaborative Study Group. UK. Intensive therapy and progression to clinical
339 albuminuria in patients with IDDM and microalbuminuria. BMJ. 1995; 311:973-77.
- 340 32. Rani PK, Raman R, Gupta A, Pal SS, Kulothungan V, Sharma T. Albuminuria and diabetic
341 retinopathy in type 2 diabetes Mellitus Sankara Nethralaya diabetic retinopathy epidemiology and
342 molecular genetic study (SN-DREAMS, report 12). Diabetol Metab Syndr. 2011; 3:9.
- 343 33. Chen H, Zheng Z, Huang Y, Guo K, Lu J, Zhang L, et al. A microalbuminuria threshold to predict
344 the risk for the development of diabetic retinopathy in type 2 diabetes mellitus patients. PLOS One.
345 2012; 7:e36718.
- 346 34. Ra H, Yoo JH, Ban WH, Song HC, Lee SS, Kim SR, et al. Predictors for diabetic retinopathy in
347 normoalbuminuric people with type 2 diabetes mellitus. Diabetol Metab Syndr. 2012; 4:29.
- 348 35. Klein R, Klein BEK, Moss SE. Prevalence of microalbuminuria in older-onset-diabetes. Diabetes
349 Care. 1993; 16:1325-29.
- 350 36. Haffner SM, Morales PA, Gruber MK et al. Cardiovascular risk factors in non-insulin dependent
351 diabetic subjects with microalbuminuria. Arterioscler Thromb. 1993; 13:205-10.