

Urinary IgG is a pure strong indicator of diabetic nephropathy than microalbuminuria in type 2 diabetic patients

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Abstract Microvascular and macrovascular complications are common in type 2 diabetes mellitus. The presence of a trace amount of albumin in the urine was originally considered a marker of renal microangiopathy but recently this concept has been challenged in several respects and microalbuminuria has been found to be associated with epithelial cell damage associated microvascular and macrovascular complications. Hence, the need to look at alternative predictive parameters. Type 2 diabetic patients with and without microvascular (retinopathy) and macrovascular (cardiovascular) complications as a class representative were selected for this study and screened for urinary excretion of microalbumin (mg/g creatinine, UACR) and IgG (mg/g creatinine, UIgGCR). The eGFR was calculated by MDRD equation and patients were sub-classified according to eGFR 60–74 ml/min/1.73 m² and eGFR ≥75 ml/min/1.73 m². The adjusted odds ratio for UACR increases significantly with secondary complications which further increases with declined eGFR up to 1.39 (95 % CI 1.26–1.53, $P<0.001$) and 1.41 (95 % CI 1.27–1.57) when adjusted for total antioxidant capacity of plasma (TAC), the adjusted odds ratio for UACR shows a higher influence on adjustment with other

traditional confounders. Whereas the odds for UIgGCR was associated with secondary complications in a selective manner, and significant only in patients shown declined renal function (eGFR 60–74 ml/min/1.73 m²) with and without secondary complications. The adjusted odds for UIgGCR in diabetic patients with microvascular and macrovascular complications was insignificant for normal renal function moreover it was 1.22 (95 % CI 1.12–1.33, $P<0.001$) and 1.21 (95 % CI 1.11–1.31, $P<0.001$) for declined renal function, which further increases if adjusted for TAC as 1.25 (95 % CI 1.13–1.37, $P<0.001$) and 1.24 (95 % CI 1.12–1.36 $P<0.001$) respectively. These results suggest that IgG could serve as stronger predictor of proteinuria over microalbumin in type 2 diabetic patients and might help to identify individuals at higher risk of diabetic nephropathy.

Keywords Diabetic microvascular and macrovascular complications · Urinary albumin · Urinary Immunoglobulin G · eGFR: estimated Glomerular Filtration Rate

Introduction

The epidemic of diabetes is increasing dramatically throughout the world affecting 285 million adults [1]. Microvascular and macrovascular complications contribute to disabilities and reduction in life expectancy in type 2 diabetes up to 75 % [2] and there is no simple solution to prevent secondary complications [3]. Therefore, early identification of symptoms of micro and macro-vascular complications has been focused. Diabetic nephropathy and retinopathy are two major microvascular complications of diabetes that share many risk factors [4]. Whereas diabetic cardiovascular diseases include clusters of macrovascular complications. The mortality rate increases

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if these complications develop together. Increment in trace amount of urinary microalbumin in diabetics was considered as hallmark of diabetic nephropathy but during the last decade it has been shown as a strong correlation with diabetic retinopathy [5, 6], and cardiovascular diseases [7]. Moreover, severity of retinopathy increases with albuminuria [8, 9]. The association of microalbuminuria with macrovascular diseases, such as coronary artery disease, stroke and peripheral arterial disease has been well established [10, 11]. In type 2 diabetics, the albumin excretion rate is a significant predictor of coronary morbidity, even after adjustment for potential confounders such as blood pressure and other cardiovascular risk factors [11]. Moreover, urinary excretion of IgG in diabetic patients has been suggested as a marker of diabetic nephropathy. Urinary excretion of microalbumin and IgG follows different mechanisms. Increased UACR may be due to increased intracapillary glomerular pressure, structural damage to the capillary barrier or tubular dysfunction. Whereas urinary excretion of high molecular weight proteins reflect abundant shunt like pore, increased glomerular basement membrane (GBM) deterioration or porosity, scanty podocyte and effacement of foot process. Present study aims to evaluate the prognostic impact of urine albumin and IgG excretion in type 2 diabetic patients showing progressive decline in eGFR, retinopathy and cardiovascular complications.

Methods

Study design and sample collection 437 patients visited the OPD once in 6 months from August 2007 to December 2010 were considered for present study. In this cross sectional study type 2 diabetic patients were selected on the basis of their current medical records referred by medical expert after detailed examination in the OPD and Diabetic Clinic of the Department of Medicine, S. K. Hospital and P. S. Medical Collage, Karamsad, Gujarat, India. All patients were fully informed about the purpose, procedure of sample collection and study. A written and informed consent was obtained after OPD consultancy this protocol was approved by research, development and ethical committee of medical college and hospital. All patients included in the study underwent a detailed questionnaire, and the maximum information was noted, including medication and control of blood glucose levels and current smoking status. Other details such as age, gender and duration of diabetes were noted at the same time. The duration of diabetes was defined as duration from the date of first time diagnosis of diabetes. The blood pressure was recorded by trained nurses in sitting position after 10 min of rest, in right arm. Patients in this study were having diabetes for at least 1 year and all the patients were on hypoglycemic drugs or insulin or a combination of both. Patients with hypertension were receiving

statin treatment. We included type 2 diabetic patients with and without secondary complications, cardiovascular diseases including coronary heart disease, previous myocardial infarction, stroke and left ventricular dysfunction. Diabetic retinopathy was considered if the patients exhibited mild to severe non-proliferative or proliferative retinal changes or macular edema with retinal thickening, in single or both the eyes. Retinopathy was examined by funduscopy and patients were considered for study if they showed symptoms of cotton wool spots, flame hemorrhages and dot-blot hemorrhages. Patients with severe illness, seizures, diabetic foot, exposure to extreme cold for long duration, strenuous exercise, anemia, pregnancy and urinary tract infection were excluded from the study. In addition, those patients who were on antibiotics or immune suppressors were also excluded. The blood and urine samples were collected in the morning session, transported cold and stored at -25°C till further use.

Biochemical and clinical parameter analysis Biochemical parameters were estimated through standard published laboratory protocols. The modified Jaffe method was used to measure serum and urine creatinine levels. The intra-assay coefficient of variation varied from 1.65 to 3.7 % [12]. Plasma protein was measured according to the method of Lowry et al. [13], Glycated hemoglobin [14], Plasma albumin and lipid profile was estimated by commercially available kits from Eve's diagnostics Ltd. India. Urinary Albumin was measured by IMMULITE auto analyzer. Total plasma antioxidative enzyme activity of Catalase [15], Super Oxide Dismutase [16], Glutathione Peroxidase [17], Paraonase [18], were measured along with total plasma protein thiol content [19]. Total plasma antioxidant capacity was measured by FRAP [20], by calorimetric method. Plasma IgG and urinary IgG were quantified using sandwich ELISA as described elsewhere [21]. All chemicals were of analytical grade and purchased from Sigma, Merck Chemicals Ltd. and antibodies for ELISA were purchased from Bangalore Genei Pvt. Ltd. India.

Data analysis The eGFR was calculated using the simplified Modification of Diet in Renal Disease (MDRD) Study Equation. $\text{MDRD-GFR (ml/min/1.73 m}^2\text{)} = 186 * (\text{serum creatinine})^{-1.154} * (\text{age})^{-0.203} (0.742 \text{ if female})$ [22]. The continuous decline in eGFR was considered if it was confirmed on two successive visits. The National Kidney Foundation Disease Outcome Quality Initiative working group defines chronic kidney diseases as a glomerular filtration rate (GFR) of less than $60 \text{ ml/min/1.73 m}^2$, and progressive diabetic nephropathy if GFR declines continuously. Therefore, we consider only those type 2 diabetic patients for study who were reported for continuous decline in renal function (1st to 2nd stage of nephropathy out of 5), $\text{eGFR} \geq 60 \text{ ml/min/1.73 m}^2$ to meet the recommended criterion [23, 24]. The three major groups of current study, diabetic nephropathy (without any other

Table 1 Demographic and clinical data of study groups

	Reference Group	Diabetic nephropathy	Diabetic retinopathy Group	Diabetic cardiovascular Group
N	50	149	142	146
Age (years)	47±7	49±10	51±10	51±11
Men %	56	55	52	56
Duration (years)	–	12±6	21±7	22±9
BMI (kg/m ²)	23.48±2.14	26.27±3.24	26.04±3.20	25.93±3.72
Smoking (%)	16	14	10	8
Fasting (mg/dl)	84.30±5.24	118.41±18.79	169.47±25.03*	168.07±26.33*
PPBG (mg/dl)	117.46±6.64	199.82±31.41	248.90±32.34*	253.69±33.43*
Glycated Hb %	5.31±0.45	7.92±0.86	9.17±2.03*	9.19±2.17*
SBP (mmHg)	114±10	138±15	148±14*	146±17*
DBP (mmHg)	74±7	78±10	86±9*	87±10*
Cholesterol (mg/dl)	141.89±40.36	178.30±45.42	207.83±42.48*	214.86±53.38*
Triglycerides (mg/dl)	128.43 (110.36–133.82)	134.44 (129.72–140.16)	155.91 (157.00–176.03)*	189.84 (178.73–203.57)*
HDL-C (mg/dl)	47.54±12.81	45.79±13.34	51.94±12.17*	50.15±13.90*
LDL-C (mg/dl)	109.68±30.99	131.19±39.42	157.22±46.71*	155.56±46.61*

Data are means ± SD or median (range). * $P < 0.001$ when compared with diabetic nephropathy group without complications; *SBP* systolic blood pressure; *DBP* diastolic blood pressure

complications and showing a continuous declined eGFR ≥ 1 ml/year), diabetic retinopathy complication and diabetic cardiovascular complications were sub-classified into two subgroups eGFR 60–74 ml/min/1.73 m² and eGFR ≥ 75 ml/min/1.73 m² respectively. The demographic and clinical data were expressed as means ± SD or medians (range). Clinical and anti-oxidative characteristic of patients were analyzed by applying ANOVA, LSD and Duncan test were set for the post hoc multiple comparison, the significance level was set at the $P < 0.05$. Multinomial logistic regression method was applied to calculate odds ratio for UACR and UlgGCR respectively, diabetic patients without any other secondary complications (eGFR ≥ 75 ml/min/1.73 m²) were set as reference category. Three models were used successively. In the first model, odds ratio was adjusted for gender and duration of diabetes and in the second model, odds ratio was adjusted for smoking, blood pressure and hyperglycemia. In

addition, in the third model, odds ratio was adjusted for total thiol content of plasma proteins and total antioxidant capacity of plasma-TAC in addition to model two. All statistical analysis were done using SPSS 17 software.

Results

Baseline clinical characteristics of study groups is shown in Table 1. All type 2 diabetic patients with a decline in renal function show a significant increase ($P < 0.001$) in metabolic parameters (blood glucose, glycated hemoglobin, blood pressure, along with plasma lipids) when compared to reference (healthy control subjects) using ANOVA. In order to determine whether these disturbed metabolic parameters have deleterious effects, we also analyzed antioxidant profile of study groups as

Table 2 Plasma antioxidant status of studied groups

	Reference Group	Diabetic nephropathy	Diabetic retinopathy Group	Diabetic cardiovascular Group
CAT (U/mg protein)	1.14±0.10	0.85±0.11	0.66±0.14*	0.75±0.15*
GLUTATHIONE (U/mg protein)	0.47±0.11	0.40±0.12	0.29±0.16*	0.30±0.15*
SOD (U/mg protein)	25.98±3.04	19.47±3.35	10.90±4.34*	11.72±5.00*
PON (nmol/min/ml)	324.36 (97.33–547.50)	210.70 (70.17–381.07)	183.87 (21.19–327.80)*	139.39 (25.35–321.86)*
TAC (μmol/L)	1053.6±85.42	839.27±100.98	688.11±128.75*	687.95±102.91*
THIOL (μmol/L)	252.78±32.56	234.44±35.72	186.12±37.86*	183.75±26.81*

Data are means ± SD or median (range). * $P < 0.001$ when compared with diabetic nephropathy group without complications; *CAT* catalase; *GLUTATHIONE* glutathione peroxidase; *SOD* super-oxide dismutase; *PON* paraoxonase; *TAC* total plasma antioxidant capacity; *THIOL* total plasma protein thiol content

shown in Table 2, The plasma antioxidant enzyme activity of Catalase, Glutathion, SOD, and Peroxinase in all diabetic patients was significantly low ($P<0.001$) when compared to reference group, this activity further decreases in diabetic patients with addition of both type of secondary complications when compared to diabetic nephropathy. Furthermore, the decreased antioxidant enzyme activity in diabetic patients with retinopathy and cardiovascular complications was not statistically different when compared to each other. Similarly, antioxidant contents, total thiol and total antioxidant capacity of plasma was significantly lower ($P<0.001$) in all diabetic patients when compared to reference group and it further decreased significantly ($P<0.001$) with diabetic secondary complications when compared to diabetic nephropathy group. Moreover, our results show that the baseline clinical characteristics and antioxidative status of enzyme activity of type 2 diabetic patients with retinopathy and cardiovascular complications were not statistically different when compared to each other.

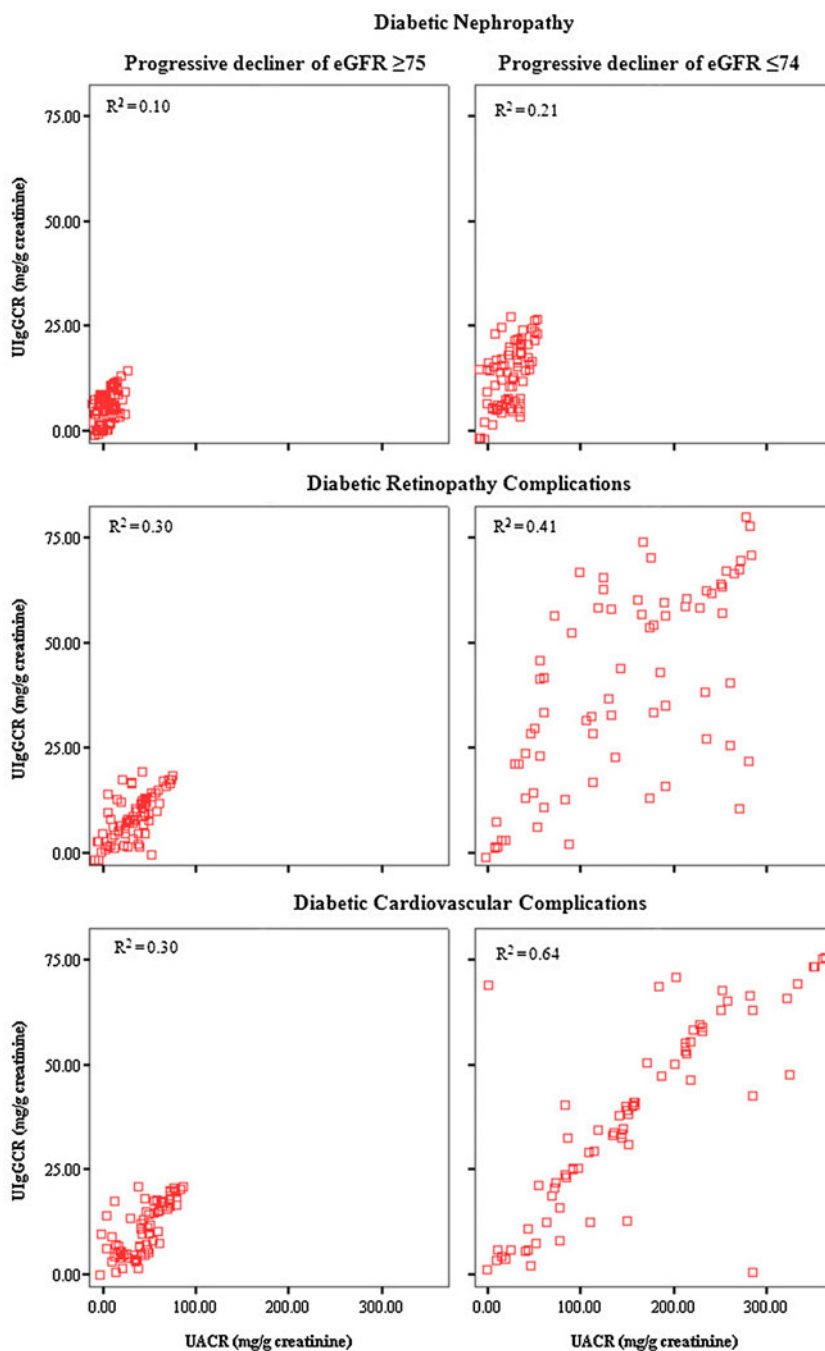
The crude values of total plasma protein, plasma albumin and IgG are shown in Table 3 with urinary excretion of albumin and IgG in studied groups. Figure 1 shows the simple regression relation between UACR and UIgGCR. The adjusted odds ratio for UACR and UIgGCR are shown in Tables 4 and 5, respectively. Moreover as shown in Table 4, odds ratio for UACR with decline in eGFR (60–74 ml/min/1.73 m²) was 1.18 (95 % CI 1.09–1.27, $P<0.001$) in model 1 which remains constant in model 2 and increased by 1.19 (95 % CI 1.08–1.31, $P<0.001$) in model 3, in type 2 diabetic nephropathy patients. There was a 10.53 % and 21.05 % increase in odds for UACR in model 2 and model 3 as compared to model 1 respectively, for diabetic patients with retinopathy and cardiovascular complications having eGFR ≥ 75 ml/min/1.73 m². The odds for UACR further increases by 25.8 %, and 32.26 % in model 2 and model 3 as compared to model 1 respectively, in diabetic patients with retinopathy and cardiovascular complication with declined renal function, (eGFR 60–74 ml/min/1.73 m²). As shown in Table 5, odds ratio for UIgGCR seemed to be associated in a selective manner and significant only with declined renal function, the odds ratio for type 2 diabetic patients, eGFR 60–74 ml/min/1.73 m² without any complications was 1.09 (95 % CI 1.01–1.18, $P<0.05$) in model 2 and 1.11 (95 % CI 1.01–1.21, $P<0.05$) in model 3 respectively and does not much differ from model 1. Furthermore, the odds ratio for UIgGCR in the diabetic patients with secondary complication and showing a higher renal function was statistically insignificant. In addition, the odds ratio for UIgGCR in model 2 and model 3 for diabetic patients with retinopathy and cardiovascular complications with decline in renal function (eGFR 60–74 ml/min/1.73 m²) were 1.22 (95 % CI 1.12–1.33, $P<0.001$), 1.25 (95 % CI 1.13–1.37, $P<0.001$) and 1.21 (95 % CI 1.11–1.31, $P<0.001$), 1.24 (95 % CI 1.12–1.36, $P<0.001$) respectively. The odds ratio for UIgGCR seems more stagnant and selectively dependent upon effectors

Table 3 Plasma and urinary proteins of study groups

	Reference Group		Diabetic nephropathy Group		Diabetic retinopathy Group		Diabetic cardiovascular Group	
	eGFR ≥ 75	eGFR 60–74	eGFR ≥ 75	eGFR 60–74	eGFR ≥ 75	eGFR 60–74	eGFR ≥ 75	eGFR 60–74
Total Plasma Proteins (g/dl)	6.87±0.52	6.67±0.79	6.67±0.79	6.53±0.80	6.53±0.80	6.16±0.75	6.17±0.65	5.85±0.83
Plasma Albumin (g/dl)	4.12±0.32	3.92±0.81	3.92±0.81	3.83±0.72	3.81±0.97	3.77±1.0	3.87±0.83	3.48±1.0
Plasma IgG (mg/dl)	844.85±30.00	1097.3±79.27	1097.3±79.27	1078.3±66.41	1019.5±103.67	987.28±98.635	1017.8±100.91	973.04±100.06
Urinary Albumin (mg/g creatinine)	3.06 (0.24–5.18)	7.65 (0.53–13.29)	7.65 (0.53–13.29)	22.76 (1.18–48.81)	34.66 (1.49–69.24)	139.25 (5.29–295.11)	46.87 (4.48–85.61)	149.52 (3.09–358.37)
Urinary IgG (mg/g creatinine)	1.8 (0.16–3.33)	6.56 (0.24–11.60)	6.56 (0.24–11.60)	14.67 (0.64–25.82)	9.60 (0.78–16.62)	38.72 (0.76–79.24)	11.88 (1.33–21.37)	38.23 (1.76–74.74)

Data are means ± SD or median (range), and eGFR expressed in ml/min/1.73 m²

Fig. 1 Correlation between UACR and UIgGCR. Figure shows the excretion pattern of urinary albumin and IgG in the type 2 Diabetic patients (Diabetic nephropathy, Diabetic retinopathy and Diabetic cardiovascular complications), the patients were divided in to two subgroups (eGFR ≥ 75 and eGFR 60–74 ml/min/1.73 m²) based on their eGFR range



(traditional confounders) in comparison of odds for UACR, as the results show the increase in odds ratio, from model 1 to model 2 and model 3 for diabetic patients with retinopathy and cardiovascular complications with declined renal function was 15.79 %, 31.57 % and 16.67 %, 33.33 % respectively.

Discussion

In type 2 diabetics, degree of hyperglycemia known to enhance micro and macro-vascular complications. Numerous

studies have shown relationship between high blood glucose and microvascular risk, particular kidney and retina [25, 26]. Uncontrolled blood glucose in diabetics with established microangiopathy accelerates microvascular lesions at the incipient stages of diabetes [27]. All traditional risk factors are ordinarily elevated in type 2 diabetes. Therefore, there is no clear discriminating impact of high blood glucose on micro or macrovascular diseases as shown in Fig. 2. The current study included the models of multivariate logistic analysis and demonstrated the association between proteinuria with stepwise adjustment by traditional confounders (main risk factors).

Table 4 Odds ratio for urinary microalbumin excretion (UACR)

Group	Significance	Odds ratio (95 % CI) Model 1	Odds ratio (95 % CI) Model 2	Odds ratio (95 % CI) Model 3
Diabetic nephropathy eGFR ≥ 75 (ml/min/1.73 m ²)	Reference NS	1	1	1
eGFR 60–74 (ml/min/1.73 m ²)	$P < 0.001$	1.18 (1.09–1.27)	1.18 (1.08–1.30)	1.19 (1.08–1.31)
Diabetic retinopathy group eGFR ≥ 75 (ml/min/1.73 m ²)	$P < 0.001$	1.19 (1.10–1.29)	1.21 (1.10–1.32)	1.23 (1.11–1.36)
eGFR 60–74 (ml/min/1.73 m ²)	$P < 0.001$	1.31 (1.21–1.42)	1.39 (1.26–1.53)	1.41 (1.27–1.57)
Diabetic cardiovascular group eGFR ≥ 75 (ml/min/1.73 m ²)	$P < 0.001$	1.24 (1.15–1.34)	1.29 (1.18–1.42)	1.31 (1.19–1.46)
eGFR 60–74 (ml/min/1.73 m ²)	$P < 0.001$	1.31 (1.21–1.42)	1.39 (1.26–1.53)	1.41 (1.27–1.57)

Model: 1; Odds calculated by multinomial logistic regression analysis and adjusted for gender and duration of diabetes, Model: 2; Odds adjusted for smoking, hypertension and hyperglycemia in addition to model1, Model 3; Odds adjusted for total antioxidants status in addition to model 2. NS; not significant

The most common aberration in diabetic patients is endothelial dysfunction. The endothelial defect leads to microalbuminuria which is a marker for a more widespread pathological process. Low grade albuminuria is representative of generalized vascular dysfunction, as a resultant of high blood pressure, lipid abnormalities, insulin resistance, endothelial dysfunction, low-grade chronic inflammation, peripheral vascular disease, and prothrombotic status [28]. Moreover, appearance of microalbumin in urine is representation of a defect in the glomerular filtration barrier, which consists of the glomerular capillary endothelium, basement membrane, and visceral epithelium. The Fig. 1 shows defect in the glomerular filtration barrier with progressive decline in eGFR in terms of albuminuria and IgG-uria which describes the regressions by univariate analysis of UACR and UIgGCR with the presence of other diabetic complications. However, the discordance of the qualitative proteinuria was more clear by multivariate logistic regression analysis. As shown in Table 4, odds ratio for UACR

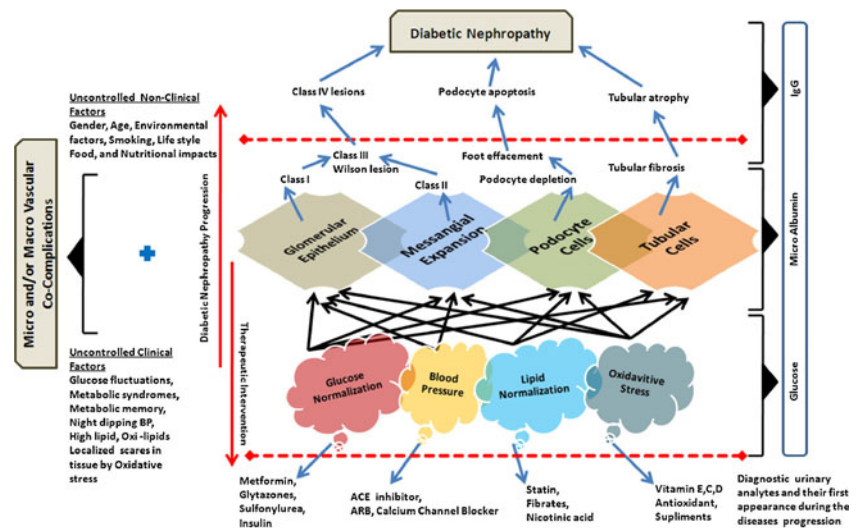
increases in model 2 and 3 when compared with model 1. The higher odd of UACR connects numerous factors involved in pathophysiology. Microalbuminuria has been related to changes in the size and charge selectivity of the GBM in diabetic patients, the charge selectivity loss has been reported earlier than defect of size selectivity [29]. Altered function has been reported due to the overt glycation which neutralizes the negative charge of glycocalyx. Damaged glycocalyx has been suggested to exhibit increased vascular protein permeability and shown a key role in retaining macromolecules [30]. This could be the explanation, why the odds for UACR significantly increases in model 2 and 3 when compared to model 1 in Table 4. Reactive oxygen species (ROS) has been reported to have potential threat to disrupt the glycocalyx, leading to proteinuria. As shown in Table 2 anti-oxidative status of diabetic patients decreases significantly in micro and macro-vascular complications, however disruption of glycocalyx has not been related to the structural changes as seen in electron microscope

Table 5 Odds ratio for urinary IgG excretion (UIgGCR)

Group	Significance	Odds ratio (95 % CI) Model 1	Odds ratio (95 % CI) Model 2	Odds ratio (95 % CI) Model 3
Diabetic nephropathy eGFR ≥ 75 (ml/min/1.73 m ²)	Reference NS	1	1	1
eGFR 60–74 (ml/min/1.73 m ²)	$P < 0.05$	1.08 (1.01–1.16)	1.09 (1.01–1.18)	1.11 (1.01–1.21)
Diabetic retinopathy group eGFR ≥ 75 (ml/min/1.73 m ²)	NS	0.93 (0.86–1.01)	0.91 (0.83–1.01)	0.93 (0.84–1.04)
eGFR 60–74 (ml/min/1.73 m ²)	$P < 0.001$	1.19 (1.11–1.28)	1.22 (1.12–1.33)	1.25 (1.13–1.37)
Diabetic cardiovascular group eGFR ≥ 75 (ml/min/1.73 m ²)	NS	0.99 (0.92–1.07)	1.01 (0.92–1.10)	1.03 (0.93–1.14)
eGFR 60–74 (ml/min/1.73 m ²)	$P < 0.001$	1.18 (1.10–1.27)	1.21 (1.11–1.31)	1.24 (1.12–1.36)

Model: 1; Odds calculated by multinomial logistic regression analysis and adjusted for gender and duration of diabetes, Model: 2; Odds adjusted for smoking, hypertension and hyperglycemia in addition to model1, Model 3; Odds adjusted for total antioxidants status in addition to model 2. NS; not significant

Fig. 2 The progression of Diabetic nephropathy and other micro and/or macro-vascular co-complications in type 2 diabetes mellitus patients. Figure shows the different stages of disease progression and first appearance of diagnostically important analytes in urine; microalbumin may be apparent at the existence or progression of other co-complications whereas IgG appears in progressive diabetic nephropathy at the commencement of serious irreversible kidney lesions



[31]. The results from the current study show that increased oxidative stress enhances proteinuria. The odds ratio for microalbuminuria was higher than IgG-uria as shown in model 3 when compared to model 1 and 2 of Tables 4 and 5 respectively. Interestingly, the percent change in odds ratio was higher for UIgGCR when compared to the UACR in declined eGFR groups (eGFR 60–74 ml/min/1.73 m²).

Hyperglycemia has been well known to increase in the production of ROS, increased NF- κ B, interfering with nitric oxide bioavailability, leading to disruption of endothelial glycocalyx [32] and Kimmelstiel–Wilson lesions. Urinary excretion of high molecular weight proteins has been suggested through increased shunt like pores and glomerular crescent formation [33]. These defects have been suggested from either loss of filtration slits bridged proteins (nephrin, α 3 β 1 integrin) or intact detachment of podocyte cell. The current study also focuses on the importance of main effectors (manageable traditional confounders) affecting qualitative proteinuria by regression models. Models in this study calculated the odds ratio for UIgGCR, which increases in model 2 and model 3 when compared to model 1 in Table 5. Noticeably, the adjusted odds for UIgGCR was insignificant in type 2 diabetic patients with higher renal function (eGFR \geq 75 ml/min/1.73 m²).

Most of the glomerular diseases cause proteinuria due to changes in the structure of the foot process intercellular junction and foot process effacement because of alteration in the podocyte cytoskeleton and migration of the podocytes over the GBM [34, 35]. Recent studies have suggested podocyte apoptosis as pivotal mechanism of type 2 diabetic nephropathy [36]. These findings are further supported by the recent studies [37], which showed that the odds ratio for plasma IgG has potential for predicting nondiabetic renal diseases in type 2 diabetic patients. Plasma level of IgG may be influenced by many factors therefore urinary IgG excretion represents the impaired renal function in more faithfully. The formations of

glomerular crescents are not easily recovered in diabetic patients and leads to high molecular weight proteinuria as shown in Fig. 2, therefore an increase in odds ratio for UIgGCR must be taken as a serious indicator of renal deterioration [38]. Abnormalities in endothelial glycocalyx have been shown in the pathogenesis of atherosclerosis, therefore emphasizing the common pathogenesis for albuminuria and cardiovascular complications [39].

The major clinical studies based on albuminuria as predictive marker have shown only a limited success and challenged by numerous studies. Recent guidelines from the National Kidney Foundation and the American Society of Nephrology (National Kidney Foundation) [40], classify patients according to their level of estimated glomerular filtration rate (GFR): the lower, the worse; the higher, the better. Studies by others on diabetic patients have shown that microalbuminuria at incipient stage is lacking correlation with GFR. Moreover, the reversal rate is noticeable in many patients from microalbuminuric to normoalbuminuric stage. Meta-analysis showed that the hazard ratios for a renal event was approximately 12 in patients with macroalbuminuria and 5 to 6 in type 2 diabetics with microalbuminuria. In addition, microalbuminuria doubles cardiovascular morbidity and mortality and all-cause mortality in type 2 diabetic patients, after correction for traditional risk factors [23]. In type 2 diabetes, the progression rate from microalbuminuria to proteinuria is 30 % in 10 years which is further confirmed by the Steno 2 study. Approximately 31 % progressed to proteinuria over 7.8 years, 31 % reverted to normoalbuminuria and remaining 38 % remained microalbuminuric. The significant rise in odds ratio for UACR with type 2 diabetic co-complications could be the reason for reversal of proteinuria to normoalbuminuria. The models similar to the current study based on UIgGCR could help the clinicians planning multifactorial therapeutic interventions targeting the main risk factors like

manageable traditional clinical confounders as shown in Fig. 2. It was concluded that microalbuminuria frequently diverges with metabolic disturbances, and more specifically with diastolic blood pressure [41]. The Microalbuminuria, Cardiovascular and Renal Outcomes in the Heart Outcomes Prevention Evaluation (MICRO-HOPE) showed that an angiotensin-converting enzyme (ACE) inhibitor, ramipril 10 mg/day, reduced cardiovascular risk by 20 % to 25 % when compared to the placebo in high-risk subjects and reduced blood pressure up to 3 mmHg (Heart Outcomes Prevention Evaluation Study Investigators) [42]. These results generate hope for preventing renal function deterioration in diabetic patients with other micro and macrovascular complications. The model 3 in Tables 4 and 5 explains why the above studies remain inefficient, even when these studies targeted strict control of main effector by multifactorial interventions.

Conclusion

The present study concludes that UACR is correlated with the secondary complications in type 2 diabetic patients with eGFR of 60 ml/min/1.73 m² or more where as UIgGCR is correlated with secondary complications in type 2 diabetic patients only with eGFR of ≥ 60 and < 75 ml/min/1.73 m². Moreover screening for UIgGCR can help to evaluate patient's nephropathy risk and guide decisions for the therapeutic interventions more accurately.

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Conflict of interest The authors declare no conflicts of interest.

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