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Evaluation of the frequency of normal to mildly increased albuminuria in patients with type 2 diabetes with CKD referred to clinics of Ahvaz teaching hospitals in the years 2014–2020

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** Diabetic nephropathy is the main cause of impaired renal function and chronic kidney disease (CKD) in diabetic patients.
Objectives. The aim of this study was to estimate the prevalence and characteristics of normal to mildly increased albuminuria in type 2 diabetes mellitus (T2DM) patients with chronic kidney disease.
Material and methods. This retrospective study was performed on 310 patients diagnosed with T2DM and renal insufficiency (eGFR < 60 mL/min/1.73 m^2) referred to Ahvaz hospitals between 2014–2020. Demographic and clinical data, as well as laboratory parameters, were extracted from patients' medical records. After considering the inclusion criteria (adult diabetic patients with renal failure (eGFR < 60 mL/min/1.73 m^2) and exclusion criteria (patients with hypertension, cardiovascular disease (ischemic heart disease, chronic heart failure, peripheral vascular disease, cerebrovascular disease), urinary tract infection, anatomical disorders of the urinary tract, kidney stones, benign prostatic hyperplasia, history of diuretic use, nephrotoxic drugs such as ACEI, ARB, NSAIDs, physiological causes of albuminuria such as prolonged standing and exercise, systematic disease (e.g. systemic lupus erythematosus) and dialysis patients), in terms of age, gender and duration of diabetes and lipid profile and retinopathy and neuropathy and HbA_{1c}, patients were divided into three groups based on the severity of albuminuria (albumin-to-creatinine ratio): normal to mildly increased albuminuria (ACR < 30 mg/g), moderately increased (ACR: 30–300 mg/g) and severely increased (ACR > 300 mg/g).
Results. A total of 310 T2DM patients with a mean age of 57.2 ± 9.5 years, including 164 women (52.9%) and 146 men (47.1%), participated in the study, of which 4 patients (1.3%) had normal albuminuria, 76 patients (24.5%) had mildly increased albuminuria, 142 patients (45.8%) had moderately increased albuminuria, and 88 patients (28.4%) had severely increased albuminuria. Individuals with normal to mildly increased albuminuria compared with moderate to severe albuminuria had lower duration of diabetes, age, creatinine, retinopathy, neuropathy, HbA_{1c}, LDL, Tchol ($p < 0.001$), higher GFR ($p < 0.001$) and lower TG ($p = 0.003$), while HDL-c ($p = 0.07$) and patients' gender ($p = 0.2$) were not significantly different. Examination of the odds ratio (OR) showed that retinopathy, high age and high HbA_{1c} levels had the greatest effect on the development of moderate to severe albuminuria, whereas increased GFR and a small increase in LDL had a preventive effect on moderate to severe albuminuria.
Conclusions. The results of the present study showed that although the majority of diabetic patients with renal insufficiency had moderate to severe albuminuria, a considerable proportion of patients with diabetes and renal insufficiency had normal to mildly increased albuminuria. This can limit the role of microalbuminuria as a screening tool to detect the onset of diabetic nephropathy.
Key words: albuminuria, chronic renal insufficiency, diabetes mellitus type 2.

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Background

Renal involvement is one of the most common complications associated with diabetes mellitus and is one of the most important causes of morbidity and mortality in diabetic patients. According to recent research, more than 40% of diabetic patients, especially type 2 diabetes, develop chronic kidney disease [1, 2]. Diabetic nephropathy is a clinical syndrome characterised by persistent albuminuria (> 300 mg/d or > 200 µg/min) and progressive decline in renal function (decreased eGFR) in diabetic patients [3, 4], as well as being the main cause of end-stage renal disease and the need for renal replacement therapy (RRT). Diabetic nephropathy is usually associated with arterial hypertension and its associated cardiovascular events and mortality [1, 2]. Diabetic nephropathy manifests itself in distinct phases and progresses from the development and progression of albuminuria from low-dose (microalbuminuria) to dominant albuminuria (macroalbuminuria) and nephrotic syndrome, ultimately leading to severe renal impairment and end stage renal disease [5, 6]. Increased urinary albumin excretion is the first sign of diabetic kidney disease, and although microalbuminuria is known as a biomarker for early diagnosis of diabetic nephrop-

athy and is routinely used [6–8], significant glomerular damage occurs before albumin is observed in the urine [9].

Renal failure is defined by a glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 [10], and a direct relationship between GFR reduction and albuminuria has been observed in patients with diabetic nephropathy [11]. However, in some diabetic patients, their GFR decreases without albuminuria [12–14]. Numerous studies have shown that decreased renal function (decreased eGFR) in diabetic patients is more likely to result from interstitial tubular injury than glomerular damage, which is a pathological change in diabetic nephropathy, and interstitial tubular fibrosis is more important in the development of normoalbuminoric diabetic kidney disease [15]. Given that in previous studies, a significant percentage of diabetic patients without albuminuria developed renal failure [16–18], it is hypothesised that albuminuria may not be a suitable marker for screening and early detection of diabetic nephropathy.

Objectives

Therefore, the aim of this study was to evaluate the frequency of normal to slightly increased albuminuria and their clinical features in type 2 diabetic patients with chronic kidney disease referred to the clinics of Ahwaz teaching hospitals. This study may help identify the role of microalbuminuria as a marker for the diagnosis of diabetic nephropathy or determine the need to use another marker for early detection and evaluation of the progression of diabetic nephropathy.

Material and methods

This retrospective descriptive-analytical study examined the records of adult patients with type 2 diabetes mellitus (DM2) and chronic kidney disease (CKD) referred to endocrinology and nephrology clinics of Imam Khomeini and Golestan hospitals in Ahwaz between the years 2014–2020. This study was conducted after obtaining permission from the Research Council and approval of the ethics committee of Ahwaz University of Medical Sciences (ethics code IR.AJUMS.HGOLESTAN.REC.1399.059). Moreover, in all stages of this research, the provisions of the ethics statement in Helsinki research and the principles of patient information confidentiality were observed. The sample size was estimated to be 256 individuals at an estimated 21% prevalence, 95% confidence, error of 0.05, using the sample size determination formula for prevalence studies based on similar previous research [16]. To ensure the prevalence of normoalbuminuria in diabetic patients with chronic renal failure, 21% was added, and the sample size was estimated at 310.

Adult diabetic patients with renal insufficiency, i.e. eGFR < 60 mL/min/1.73 m^2, were included in the study. The diagnosis of diabetes mellitus was made according to WHO and American Diabetes Association (ADA) criteria [19], which are: fasting blood sugar (FBS) ≥ 126 mg/dl; oral glucose tolerance test (OGTT) ≥ 200 mg/dl; HbA_{1C} ≥ 6.5%, classic symptoms of hyperglycaemia with BS ≥ 200 mg/dl. Patients with hypertension, cardiovascular disease (ischemic heart disease, chronic heart failure, peripheral vascular disease, cerebrovascular disease), urinary tract infection, anatomical disorders of the urinary tract, kidney stones, benign prostatic hyperplasia, history of diuretic use, nephrotoxic drugs such as ACEI, ARB, NSAIDs, physiological causes of albuminuria such as prolonged standing and exercise, systematic disease (e.g. systemic lupus erythematosus) and dialysis patients were excluded due to confounding factors. Additionally, to rule out the possibility of glomerulonephritis, the urine analysis (urinalysis, U/A) of patients was examined for pyuria, haematuria or cysts, and if any, they were excluded from the study.

Data collection

This retrospective study was performed as a case study and review of patients' demographic and laboratory information. First, the basic characteristics of all subjects, including demographic and clinical information such as age, gender and duration of diabetes, were collected and recorded. Experiments including serum creatinine and lipid profiles (LDL-C, HDL-C, total cholesterol and triglycerides), HbA_{1C} and albumin to random morning creatinine (ACR) albumin levels were extracted from patients' records for albuminuria. Glomerular filtration rate (GFR) was also calculated for patients using the CKD-EPI formula. Information on retinopathy and diabetic neuropathy was also collected from patients' records, if any.

Based on the recommendations of KDIGO (2012) guidelines for CKD, three classes were used to describe the severity of albuminuria in this study [20]. This classification based on urinary albumin-to-creatinine ratio (ACR) is as follows: ACR values < 3 mg/mol or 30 mg/g indicate "normal to mildly increased albuminuria"; ACR values between 3 and 30 mg/mol or 30 to 300 mg/g indicate "moderately increased albuminuria"; ACR values > 30 mg/mmol or 300 mg/g indicate "severely increased albuminuria" [18, 20].

Statistical analysis

SPSS software (SPSS Inc., Chicago, IL, U.S.A.) version 24 was used for statistical analysis. Mean and standard deviation were used to describe the data in quantitative variables and frequency, and percentages were used in qualitative variables. Data normality was assessed by the Kolmogorov-Smirnov test, and homogeneity of variance was assessed by the Leven test. The independent *t*-Test, analysis of variance and Chi-square test were used to compare and analyse the data. The logistic regression model and determination of risk ratio (odds ratio) in a 95% confidence interval were also used to evaluate the predictive factors of moderate to severe albuminuria. The significance level was considered as 0.05 in the tests.

Results

In this study, 310 patients with type 2 diabetes with a mean age of 57.2 ± 9.5 (range 33–86 years), including 164 women (52.9%) and 146 men (47.1%), participated. Among them, 4 patients (1.3%) had normal albuminuria, 76 patients (24.5%) had slightly increased albuminuria, 142 patients (45.8%) had moderate albuminuria, and 88 patients (28.4%) had severe albuminuria. The two groups of normal and slightly increased al-

Table 1. Comparison of laboratory and clinical variables of patients at three different levels of albuminuria

Parameter	Total *n* = 310	Normal to mildly increased albuminuria (*n* = 80)	Moderately increased albuminuria (*n* = 142)	Severely increased albuminuria (*n* = 88)	*p**
Sex (woman)	164 (52.9)	47 (58.7)	68 (47.9)	49 (55.7)	0.246
Age (year)	57.2 ± 9.5 (33,86)	49.3 ± 7.1 (33,66)	57.0 ± 7.8 (37,76)	64.8 ± 8.0 (43,86)	< 0.001
Diabetes duration (years)	8.5 ± 3.9 (2,30)	6.0 ± 2.2 (2,15)	8.3 ± 3.2 (3,20)	11.2 ± 4.5 (5,30)	< 0.001

Table 1. Comparison of laboratory and clinical variables of patients at three different levels of albuminuria

Parameter	Total *n* = 310	Normal to mildly increased albuminuria (*n* = 80)	Moderately increased albuminuria (*n* = 142)	Severely increased albuminuria (*n* = 88)	*p**
Creatinine (mg/dl)	1.7 ± 0.5 (1.1,4.2)	1.3 ± 0.1 (1.1,1.8)	1.6 ± 0.4 (1.2,4)	2.1 ± 0.5 (1.2,4.2)	< 0.001
GFR (CKD-EPI) (ml/min/1.73 m^2)	39.8 ± 12.2 (11,59)	51.5 ± 5.7 (30,59)	39.8 ± 10.4 (11,59)	29.2 ± 9.3 (12,57)	< 0.001
HbA_{1c} (%)	7.2 ± 0.8 (5.5,10.5)	6.6 ± 0.6 (5.5,8.5)	7.2 ± 0.7 (5.9,10.2)	7.7 ± 0.7 (6.3,10)	< 0.001
HDL Cholesterol (mg/dl)	43.6 ± 6.7 (30,76)	45.1 ± 6.7 (31,60)	43.2 ± 7.5 (30,76)	42.9 ± 5.0 (32,59)	0.072
LDL Cholesterol (mg/dl)	121.9 ± 27.5 (71,211)	116.8 ± 26.8 (71,178)	116.6 ± 23.5 (71,198)	135.0 ± 29.8 (73,211)	< 0.001
Total Cholesterol (mg/dl)	196.8 ± 36.6 (91,360)	182.3 ± 33.1 (91,270)	196.6 ± 36.2 (109,360)	210.2 ± 35.4 (124,314)	< 0.001
TG Cholesterol (mg/dl)	194.4 ± 54.4 (87,418)	179.6 ± 53.9 (95,417)	194.0 ± 55.3 (87,418)	208.4 ± 50.3 (128,330)	0.003
Retinopathy	171 (55.2)	7 (8.7)	77 (54.2)	(98.9)	< 0.001
Neuropathy	164 (52.9)	14 (17.5)	70 (49.3)	80 (90.9)	< 0.001

Numbers are presented as mean ± standard deviation or frequency (percentage). * $p < 0.05$ is significant.

Table 2. Relationship between clinical risk factors and moderate to severe albuminuria (logistic regression model and odds ratio)

Clinical risk factors	Odds ratio Exp (B)	95% confidence interval (lower-upper)	*p*
Retinopathy	3.478	1.092–11.075	< 0.001
Male	8.833	1.465–53.244	0.24
Age	1.084	1.007–1.167	< 0.001
Creatinine	0.408	0.006–29.089	< 0.001
GFR	0.785	0.681–0.905	< 0.001
HbA_{1C}	3.230	1.424–7.329	< 0.001
HDL	0.972	0.913–1.034	0.07
LDL	0.969	0.947–0.991	< 0.001
TG	0.998	0.998–1.008	0.003
T. Chol	1.013	0.997–1.029	< 0.001
Diabetes duration	1.002	0.804–1.248	< 0.001
Neuropathy	0.385	0.108–1.371	< 0.001

buminuria were analysed together in one group. A comparison of patient profiles at three different albuminuria levels is presented in Table 1. Individuals with normal to slightly increased albuminuria had a shorter duration of diabetes, lower age, creatinine, retinopathy and neuropathy, lower HbA_{1c}, LDL, Tchol ($p < 0.001$) and higher GFR ($p < 0.001$) and lower TG ($p = 0.003$) in comparison with patients with moderate to severe albuminuria, whereas evaluating HDL ($p = 0.07$) and the gender of patients ($p = 0.2$) showed no significant difference (Table 1). Odds ratio evaluation showed that retinopathy, high age and high HbA_{1c} had the greatest effect on the development of moderate to severe albuminuria, whilst high GFR and low LDL appeared to have a preventive effect against moderate to severe albuminuria development (Table 2).

Discussion

The results of the present study showed that the majority of diabetic patients with renal failure had moderate to severe albuminuria. 45.8% had moderate albuminuria, and 28.4% had severe albuminuria, whilst 1.3% of the patients had normal albuminuria, and 24.5% had mildly increased albuminuria. This study showed a significant percentage of normal albuminuria in diabetic patients is accompanied by renal insufficiency, but this prevalence is different in various studies. Differences in the characteristics of the study population and the sample under study and the study plan can be the cause of differences in the results. Moreover, these differences in the results show that kidney disease in type 2 diabetic patients depends on different factors, and different mechanisms can play a role in albuminuria and renal dysfunction. In addition, the high prevalence of non-albuminuria CKD in diabetic patients indicates the importance of investigating and identifying other factors to diagnose and predict renal failure in diabetic patients. Based on the results of cross-sectional descriptive and cohort studies, the prevalence of renal failure with normoalbuminuria in diabetic patients is not very uncommon, and this rate has been reported to be between 14% and 57% in studies conducted in different countries [8, 21–23]. The results of Shikata et al.'s study in Japan showed that the prevalence of normoalbuminuria in type 2 diabetic patients with renal failure (eGFR < 60 mL/min/1.72 m^2) was 9%, and high albuminuria was reported as a risk factor for renal failure in diabetic patients [23]. However, in another study in Japan,

a higher prevalence (51.8%) of normoalbuminuria was reported in diabetic patients with renal failure [22]. In Boronat et al.'s study of 78 type 2 diabetic patients with renal failure, 21.8% of patients had normoalbuminuria, 20.5% had microalbuminuria, and 57.7% had macroalbuminuria [16]. The results of Liyanage et al.'s study showed that 26.7% of diabetic patients had normoalbuminuria despite renal failure, which limits the role of albuminuria as a screening tool for early diagnosis of diabetic nephropathy [8]. One of the reasons for the difference of the present study is that our study examined only diabetic patients with renal insufficiency, whereas Liyanage's study examined all diabetic patients without renal function, and microalbuminuria was considered as urinary albumin excretion > 30 mg/g, and lower values were considered normal. In the present study, the severity of albuminuria was classified. Furthermore, in a study by Aristizábal Gómez et al. on 63 patients with type 2 diabetes mellitus and no albuminuria, 75.75% of patients were reported to have normal albuminuria, and 49.3%, a moderate increase in albuminuria (microalbuminuria) [24]. In the study of Laranjinha et al. on 146 patients with type 2 diabetes with non-albuminouric diabetic kidney disease with GFR > 75 ml/min/1.73 m^2, 53.4% of patients with diabetic albuminuria and 46.6% of diabetic patients with renal disease were non-albuminouric [25]. In Kodgirwar's study, the prevalence of non-albuminouric CKD was 1.5 times higher in diabetic patients (11.3% vs 7.5%) compared to albuminouric CKD [presence of protein in urine (positive dipstick test)] [26]. CKD with normal albuminuria can occur in tubulointerstitial disease histopathological diagnosis, which is characterised by a lack of significant proteinuria, absence of overt clinical oedema and no known cause of chronic renal failure [15, 27]. This indicates the need for screening for renal failure and the onset of diabetic nephropathy in diabetic patients with normoalbuminuria [8, 26]. In the present study, diabetic retinopathy was present in only 8.3% and neuropathy in 17.5% of patients with normal to slightly increased albuminuria. Patients with normal to mild albuminuria also had better glycaemic control (HbA_{1c}) and better lipid profiles than those with moderate to severe albuminuria. The finding that normal to slightly elevated albuminuria is not significantly associated with other diabetic microvascular risk factors and that most risk factors are associated with higher albuminuria levels has been reported in other previous studies [16, 26]. In the Liyanage study, 96.7% of diabetic patients with normoalbuminuria with renal failure had no retinopathy, and 76.9% of them had no neuropathy [8]. A study in Italy reported that retinopathy is present in only 23.5% of diabetic patients with renal failure with normoalbuminuria [14]. 75.6% of normoalbuminuria patients were also reported to have no other microvascular complications [28]. Based on the results of the present study, old age, longer duration of diabetes, high serum creatinine, low GFR, high HbA_{1c} levels, lipid disorders in the form of LDL, TG and total cholesterol levels, as well as the presence of diabetic retinopathy and neuropathy, were predictive of severe to moderate albuminuria, of which the presence of retinopathy, old age and high HbA_{1c} had the greatest effect, and increased LDL and increased GFR had a preventive effect against albuminuria development, particularly moderate to severe albuminuria. Similar results have been reported in other studies. In the study of Bonakdaran and Armanpour, old age, longer duration of diabetes, high glycosylated haemoglobin levels and the presence of retinopathy were independent risk factors for micro- and macroalbuminuria and diabetic nephropathy [17]. In the study by Shikata et al., albuminuria-related risk factors included HbA_{1c}, hypertension, dyslipidaemia, old age, long duration of diabetes, eGFR and high body mass index [23]. In Liyanage et al.'s study, age, duration of diabetes, high systolic blood pressure, poor glycaemic control (high HbA_{1C}) and high BMI were among the risk factors for albuminuria in diabetic patients with renal insufficiency [8]. These results are consistent with the findings of the present study. In the study by Boronat et al., diabetic patients with chronic normalbuminuria renal failure were reported to have lower serum creatinine, lower total cholesterol and LDL, as well as lower $HbA_{1C,}$ than the micro- and macroalbuminuria groups [16]. Consideration and evaluation of the mentioned risk factors can be helpful in management of the patients. In other studies, increased duration of diabetes and old age have been reported as risk factors for more advanced stages of diabetic nephropathy [8, 17, 29]. These results suggest that some diabetic patients may initially develop renal failure without albuminuria and later progress to microalbuminuria as the disease progresses.

Finally, the present study, based on hospital information, was performed on adult diabetic patients with renal insufficiency and showed a high prevalence of albuminuria compared to other studies. Most previous studies (both hospital-based and population-based) show a lower prevalence of albuminuria. Differences in the prevalence of albuminuria and its severity of risk factors in different populations can be related to differences in the study population, study design and definitions of study variables. The most important strengths of the present study were the appropriate sample size, albuminuria division into four groups of normal, slightly increased, moderately increased and severely increased, as well as comparing the relationship between albuminuria severity and patients' clinical characteristics. Moreover, in this study, patients with predisposing factors for renal failure other than diabetes and the possibility of glomerulonephritis such as hypertension, cardiovascular disease, urinary tract abnormalities, kidney stones, benign prostatic hyperplasia and systematic disease, as well as dialysis patients, were excluded from the study due to confounding factors. On the other hand, the present study also faced some limitations, including the fact that due to the incompleteness of the files and the distortion of some information within the hospital records, it was not possible to evaluate some information.

Conclusions

The results of the present study showed that although the majority of diabetic patients with renal failure had moderate to severe albuminuria, 1.3% had normal albuminuria, and 24.5% had slightly increased albuminuria, which is still a significant number. This could limit the role of microalbuminuria in screening and detecting the onset of diabetic nephropathy. Therefore, it is important to identify other methods for early detection and evaluation of the progression of diabetic nephropathy along with microalbuminuria.

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