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Mahmoud El Mezayen
Department of Internal Medicine, Faculty of Medicine, Tanta University, Egypt

Fayza Lasheen
Department of Internal Medicine, Faculty of Medicine, Tanta University, Egypt

Muhammed Tarek
Department of Clinical Pathology, Faculty of Medicine, Tanta University, Egypt

Ghada Al Ghazaly
Department of Internal Medicine, Faculty of Medicine, Tanta University, Egypt

Manal Negm
Department of Internal Medicine, Faculty of Medicine, Tanta University, Egypt

Corresponding Author:
Mahmoud El Mezayen
Department of Internal Medicine, Faculty of Medicine, Tanta University, Egypt

Urinary transferrin as an early Marker of Diabetic Nephropathy

Mahmoud El Mezayen, Fayza Lasheen, Muhammed Tarek, Ghada Al Ghazaly and Manal Negm

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Abstract
Back ground: The Diabetic Kidney Disease (DKD) prevalence is increasing, making it a major healthcare issue. Early detection of DKD is a challenging medical concern. Urinary transferrin is a glycoprotein with low molecular weight and negatively charged ionic load making it simply filtered via renal glomeruli, so its levels increase even with normal albumin creatinine ratio in diabetic nephropathy (DN).
Objectives: We examined the level of urinary transferrin across instances with type 2 diabetes mellitus (T2DM) to assess its validity as early markers for diabetic nephropathy.
Methods: In this cross-sectional work, we tested 200 subjects, (50 healthy control, 50 normoalbuminuric T2DM patients, 50 microalbuminuric T2DM patients and 50 macroalbuminuric T2DM patients) recruited from Internal Medicine Department, Tanta University Hospitals. Patients evaluated for urinary transferrin that had been evaluated utilising enzyme-linked immunosorbent assay (ELISA).
Results: urinary transferrin was significantly increased among diabetic patients even with normal albumin creatinine ratio and their levels elevated more with more elevation of albumin creatinine ratio.
Conclusion: Urinary transferrin ought to be used as early markers for DN and this will provide early diagnosis and prompt intervention in these patients.

Keywords: Diabetic kidney disease, diabetic nephropathy and early detection, Urinary transferrin

Introduction

DN or DKD is one of micro vascular consequences of diabetes mellitus (DM) with high morbidity and fatality [1].

DN isn't only the most prevalent form of chronic kidney diseases (CKD) as about 40% of DM individuals develop DKD but also the primary cause of end stage renal disease (ESRD) globally [1-5].

The clinical hallmark of DN has been albuminuria and it was believed to develop before renal function loss [6-8].

Based on that classical belief albumin creatinine ratio (ACR) is a well-standardised urinary marker for detection of DN in clinical practice [9].

However, both albuminuria and e GFR are insufficiently sensitive to ascertain kidney impairment in DN as there is growing evidence that some individuals with DM have renal function loss in the lack of overt albuminuria [10-16].

Also, the affection of e GFR and the development of albuminuria occur to some extent at late stage giving rise to the need of novel markers to identify DN at earlier stages [17].

In recent years, many glomerular and tubular urine biomarkers, particularly urinary transferrin (TF), have been investigated in individuals with DM. Despite the alteration of these urine indicators in DN, their significance for early diagnosis and their correlation to severity of DN and also their association with e GFR alteration and albuminuria hasn't been assessed [18].

Hence, our work aimed to measure the levels of urinary TF as glomerular marker in DN and to analyze their association with e GFR and albuminuria.

Patients and Methods

In this observational cross-sectional work, 50 healthy people served as the control group (group I), whereas 150 patients over the age of 18 with T2DM depending on American diabetes association (ADA) criteria [19, 20] served as the case group. Patients were separated depending on ACR to three groups (group II, III, IV) normo, micro and macroalbuminuric, and then they were compared. From 2022 to 2023, subjects had been gathered from Tanta University Hospitals' Nephrology Unit, Internal Medicine Department. Prior to the study, patients with malignancy, history of smoking, with other renal diseases which includes (glomerulonephritis, infections, nephrolithiasis), who take nephrotoxic drugs, with congestive heart failure, dialysis patients and pregnant women were excluded.

The patient's group had been exposed to the following:

Comprehensive taking of history

Full examination of the patients

- **Abdominal ultrasound:** for any abnormalities and grading of nephropathy.
- **Laboratory tests that includes:** Complete blood count (CBC) with differential count, fasting blood glucose (FBG), 2 hours postprandial blood glucose (2 hr pp), Hemoglobin A1c (HbA1c), Lipid profile including (total cholesterol and triglycerides), Serum creatinine, Serum albumin, Urinary ACR, Estimated GFR, Urinary transferrin.

Sampling

- 10 ml of peripheral blood sample was withdrawn under complete aseptic conditions using sterile vacutainers and divided as the following:
- 2 ml into k3-EDTA vacutainer tube for CBC and HbA1c.
- The remaining blood was collected in a tube was used immediately for routine laboratory investigation including (FBG 2hr PP cholesterol triglycerides serum albumin serum creatinine).

- **The eGFR** had been determined Using The 2021 CKD-EPI equation, currently the approved standard, excludes race, unlike the 2009 and 2012 CKD-EPI creatinine and creatinine-cystatin C equations. [21]

  Articulated as a singular equation: eGFRcr = 142 x min (Scr/κ, 1) α x max(Scr/κ, 1) - 1.200 x 0.9938 Age x 1.012 [if female]

  where: Scr = standardized serum creatinine in mg/dL, κ = 0.7 (females) or 0.9 (males), α = -0.241 (females) or -0.302 (males), min (Scr/κ, 1) denotes the lesser value between Scr/κ and 1.0, max (Scr/κ, 1) denotes the greater value between Scr/κ and 1.0, age (years).

Urinary albumin / creatinine ratio

Sampling

Spot urine samples have been obtained in a sterilised container and subjected to centrifugation for 20 mins at a velocity of 2000-3000 r.p.m.

Method

Urinary albumin absorbance was measured by turbidimetric method using ERMA INC photometer model AE-600n, (Japan).

Urinary albumin concentration was calculated using Bear's law

(Absorbance of sample/ absorbance of standard = concentration of sample/concentration of standard).

Urinary creatinine concentration was measured by kinetic method using fully automated EN Konelab / T Series analyser (Thermo Fisher Scientific Oy, Finland) after sample dilution 50 times (2450 µl distilled water + 50 µl of urine sample).

Urinary transferrin

Urinary transferrin was estimated by Enzyme-linked immune-sorbent assay (ELISA) kit by wuxi donglin Sci &Tech Development Co., Ltd. made in China supplied by Biokit Egypt, (Catalog No: EDL 2024013113, develop company, china)

Principle of the assay

The kit employs a double-antibody sandwich ELISA to measure the concentration of Human transferrin (TF) in samples. This kit includes a microtiter plate that has been pre-coated with an antibody specific to TF. Standards or samples are thereafter inputted into the designated microtiter plate wells containing a biotin-conjugated antibody preparation specific to TF. Afterwards, Avidin conjugated with Horseradish Peroxidase (HRP) is added to each microplate well and provided for incubation. Only the wells containing TF, biotin-conjugated antibody, and enzyme-conjugated avidin will exhibit a color shift with the introduction of the TMB substrate solution. The enzyme-substrate reaction is terminated by the addition of sulfuric acid solution, and the colorimetric alteration is measured spectrophotometrically at a wavelength of 450 nm ± 10 nm. The TF concentration in the samples is determined by comparing their optical density to the reference curve.

Detection Range

1.56-100ng/mL. The concentrations for the standard curve employed in the ELISA had been 100 ng/mL, 50 ng/mL, 25 ng/mL, 12.5 ng/mL, 6.25 ng/mL, 3.12 ng/mL, and 1.56 ng/mL.

Ethical consideration

- An informed written consent had been collected from all participants following the elucidation of the research design, anticipated benefits and possible risks.
- We hide the name of the patient when we use the research.
- The findings of the work had been utilised only in scientific purposes and not used for any other aims.
- There was a code number for each patient, so data of patients will be strictly confidential.
- Any unexpected risks were notified to the patients and ethical committee on time.

Study approval.

Approval was secured from the Research Ethical Committee under the Quality Assurance Unit of the Faculty of Medicine at Tanta University to do this research and use the hospital's resources. (Approval code 35748/9/22)

Statistical analysis

The gathered data had been organized, tabulated, and statistically analysed employing the IBM® SPSS statistical software, version 21 (Statistical Package for Social Studies) generated by IBM, Illinois, Chicago, USA. We utilised the one-sample Kolmogorov-Smirnov test to assess the data normality and some of data had been parametric and other were non-parametric. In this work, the qualitative data had been represented utilising numbers and percentages. Quantitative factors had been displayed as mean and standard deviation (SD) or median and interquartile range (IQR). P value of ≤ 0.05 had been utilised as a cut off value for significance of results.

The tests utilized had been: Chi-square test for categorical parameters for comparing between various groups, Independent sample t-test for normally distributed quantitative parameters to contrast among two studied groups, Monte Carlo test for Correction for chi-square when >20% of the cells have expected count <5, F-test (ANOVA) for normally distributed quantitative parameters, to contrast between > two groups, K (Kruskal Wallis test) for abnormally distributed quantitative parameters to contrast between > two groups, Post Hoc test (Scheffe test) for pairwise comparisons to detect the significance between groups, Mann Whitney test for abnormally distributed quantitative parameters to contrast between two studied groups, Spearman correlation coefficient (rs) used to show the direction and strength of the relationship between two variables (continuous or categorical), Receiver operating characteristic curve (ROC) for the sensitivity and specificity of each parameter measured and Multiple linear regression for the association between variables, and quantifying the relationship between more than one predictor variable.

Results

- In our study the population age ranged from 35 to 72 years in case group, and from 33 to 70 years in control group with no statistically significant variation among both groups as regarding age (p value 0.423) and the studied population included 79 males with 71 females in case group and 25 males with 25 females in control group with no statistically significant variations among both groups as regarding sex (p value 0.744). table 1
- The studied population hemoglobin level in case group ranged from 7.1 to 17.7 g/dl, and from 11.5 to 16 g/dl in control group with no statistically significant variations among both groups as regards hemoglobin level (p value 0.062).
- The studied population platelet count ranged from 110000 to 420000 /mm^3 in case group, and from 150000 to 450000 / mm^3 in control group with no statistically significant variations among both groups as regarding platelet count (p value 0.812).
- The studied population total leucocytic count in case group ranged from 1400 to 14200 /mm^3 and from 4200 to 11800/ mm^{3}in control group with no statistically significant variations among both groups as regarding total leukocytic count (p value 0.563).
- Fasting blood glucose increased in case group (100 to 400 mg/dl) with mean 175.4± 63.8 mg/dl than in control group (75 to104) with mean 93.2± 8.8 mg/dl with statistically significant variations among both groups as regarding fasting blood glucose (p value <0.001).
- Two hours post prandial blood glucose level increased in case group (119 to 525 mg/dl) with mean 236.4± 81.1 mg/dl than in control group (101 to 150 mg/dl) with mean 125.4± 15.1 mg/dl with statistically significant variations among the two groups as regarding two hour post prandial blood glucose (p value <0.001).
- Hemoglobin A1c increased in case group ranged from 6 to 16.6 with mean 9.9± 2.3%than in control group ranged from 4.2 to 5.4% with mean 4.7± 0.3% with statistically significant variations among both groups as regarding hemoglobin A1c (p value <0.001).
- Total cholesterol level increased in case group with range between 100 to 400 mg/dl and mean of 220.6± 69.4 mg/dl than in control group with range between 108 to 180 mg/dl and mean of 137.9± 23.1 mg/dl with statistically significant variations among both groups as regarding total cholesterol level (p value <0.001).
- Triglycerides level increased in case group with range between 85 to 400 mg/dl and mean of 158.8± 51.1 mg/dl than in control group with range between 90 to 140 mg/dl and mean of 104.7± 16.2 mg/dl with statistically significant variations among both groups as regarding triglycerides level (p value <0.001).
- Serum albumin level decreased in case group with range between 2.1 to 5 g/dl and mean of 4.0± 0.4 g/dl than in control group with range between 3.8 to 5.2 g/dl and mean of 4.5± 0.4 g/dl with statistically significant differences between the two groups as regarding serum albumin level (p value <0.001).
- Serum creatinine increased in case group with range of 0.5 to 4.8 mg/dl and median of 1 mg/dl than in control group with range of 0.5 to 1 mg/dl and median of 0.8 mg/dl with statistically significant variations among both groups as regarding serum creatinine level (p value <0.001).
- Estimated glomerular filtration rate decreased in case group with range between 10.1 to 135.1 ml/min/1.73m^3 and median of 83.1 ml/min/1.73m^3 than in control group with range between 90.6 to 157.8 ml/min/1.73m^3 and median of 104 ml/min/1.73m^3 with statistically significant variations among both groups as regarding Estimated glomerular filtration rate (p value <0.001).
- Urinary albumin creatinine ratio increased in case group with range between 6 to 7853 mg/g and median of 143 mg/g than control group with range between 2 to 25 mg/g and median of 10 mg/g with statistically significant variations among both groups as regarding urinary ACR (p value <0.001).
- Renal transabdominal ultrasonography was normal as regard echogenicity, corticomedullary differentiation and size in all control group population and the same in case group population except 2 cases with grade I nephropathy and 6 cases with grade II nephropathy with no statistically significant differences between the two groups as regarding renal transabdominal US (p value 0.239).
- Urinary transferrin level increased among case group with range between 1.31 to 100 ng/ml and median of 7.5 ng/ml than control group with range between 0.8 to 1.4 ng/ml with median of 1.2 ng/ml with statistically significant variations among both groups as regarding urinary transferrin level (p value <0.001). table2
- In table 3 urinary transferrin in group II range from 1.3 to 50.9 ng/ml with median of 15.5 ng/ml and in group III range from 1.95 to 11.9 ng/ml with median of 3

ng/ml and in group IV from 1.7 to 100 ng/ml with median of 13.3 ng/ml with statistically significant differences between group III and IV (p3 value <0.001).

- In table 4 A statistically substantial positive moderate correlation between urinary TF and urinary albumin creatinine ratio in case groups (p value <0.001) and also significant positive moderate correlation between urinary TF and urinary albumin creatinine ratio in group IV (p value <0.001).
- In table 5 A statistically significant negative moderate correlation existed between urinary transferrin and estimated GFR in case groups (p value <0.001) and also significant negative strong correlation between urinary transferrin and estimated GFR in group II (p value <0.001) and also significant negative moderate correlation between urinary transferrin and estimated GFR in group IV (p value <0.001).
- In table 6 the cut off value of urinary transferrin to discriminate between group I and II was > 2.25 ng/ml with sensitivity 88%, specificity 100%, with statistically significant variations among both groups (p value <0.001) while to discriminate between group II and III was > 2.99 ng/ml with sensitivity 88%, specificity 50%, with statistically significant variations among both groups (p value <0.001) while the cut off value to discriminate between group III and IV was > 3.39 ng/ml with sensitivity 80%, specificity 58%, with statistically significant variations among both groups (p value <0.001).

Table 1: Comparison between cases and control groups regarding age and sex.

Variable	Cases groups (n=150)	Control group (n=50)	Test of sig.	P
Age (Years)			T 6.512	0.423
Range	35 - 72	33 - 70		
Mean± SD	49.4± 13.9	46.1± 9.2		
Sex/ frequency (%)			χ^2 0.107	0.744
Male	79(52.7)	25(50.0)		
Female	71(47.3)	25(50.0)		

Table 2: Comparison between cases and control groups regarding different measured variables.

Variable	Cases groups (n=150)	Control group (n=50)	Test of sig.	P
Hemoglobin g/dl (HB)				
Range	7.1 - 17.7	11.5 - 16.0	0.713	0.062
Mean± SD	12.3± 2.6	13.4± 1.7		
Platelet Count (PLT) × 10^3/ mm^3				
Range	110 - 420	150 - 450	0.571	0.812
Mean± SD	257.2± 71.0	295.4± 155.2		
Total Leucocytic Count (TLC) / mm^3				
Range	1400 - 14200	4200 - 11800	0.729	0.563
Mean± SD	7029.3± 3196.3	7940.0± 1813.7		
Fasting Blood Sugar (FBS) (mg/dl)				
Range	100 - 400	75 - 104	-15.330	<0.001*
Mean± SD	175.4± 63.8	93.2± 8.8		
2HRPP (mg/dl)				
Range	119.0 - 525.0	101 - 150	-15.957	<0.001*
Mean± SD	236.4± 81.1	125.4± 15.1		
Hb A1C (%)				
Range	6.0 - 16.6	4.2 - 5.4	-15.425	<0.001*
Mean± SD	9.9± 2.3	4.7± 0.3		
Cholesterol (mg/dl)				
Range	110 - 400	108 - 180	-12.634	<0.001*
Mean± SD	220.6± 69.4	137.9± 23.1		
Triglycerides (mg/dl)				
Range	85 - 400	90 - 140	-11.342	<0.001*
Mean± SD	158.8± 51.1	104.7± 16.2		
Serum albumin(g/dl)				
Range	2.1 - 5.0	3.8 - 5.2	6.181	<0.001*
Mean± SD	4.0± 0.4	4.5± 0.4		
Serum creatinine (mg/dl)				
Range	0.5 - 4.8	0.5 - 1.0	(U)	<0.001*
Median (IQR)	1.0(0.8 - 1.2)	0.8(0.7 - 0.9)	1928.0	
Estimated GFR (ml/min/1.73m^3)				
Range	10.1 - 135.1	90.6 - 157.8	(U)	<0.001*
Median (IQR)	83.1(58.4 - 98.8)	104.0(99.9 - 114.3)	1933.0	
Albumin/ creatinine ratio (mg/g)				
Range	6.0 - 7853	2 - 25	(U)	<0.001*
Median (IQR)	143.0(22.0 - 580.0)	10.0(7.0 - 25.0)	998.0	
Renal US/ Frequency (%)				
Normal	142(94.7)	50.0(100.0)	MC	0.239
Grade1	2(1.3)	0(0.0)		

Grade 2	6(4)	0(0.0)		
Urinary transferrin(ng/ml)				
Range	1.31 - 100.0	0.8 - 1.4	(U)	<0.001*
Median (IQR)	7.5(2.89 - 25.9)	1.2(0.9 - 1.3)	36.0	

t: Independent sample t test U: Mann Whitney test MC: Montecarlo test P: significant at ≤ 0.05

Table 3: Comparison between case groups regarding urinary transferrin.

Variable	Group II (n=50)	Group III (n=50)	Group IV (n=50)	Test of sig.	P
Urinary transferrin(ng/ml)				K 33.502	<0.001*
Range	1.3 - 50.9	1.95 - 11.9	1.7 - 100.0		
Median (IQR)	15.5(5.0 - 28.8)	3.0(2.3 - 6.1)	13.3(4.7 - 38.4)		
Scheffe test	P3: <0.001*				

P3: Group III versus Group IV

Table 4: Correlation between Albumin/ Creatinine ratio (ACR), urinary transferrin in general and among different groups

Correlation	Albumin/ Creatinine ratio (ACR)	
	Rs	P
Urinary Transferrin	0.428	<0.001*
Group II	0.273	0.055
Group III	0.127	0.379
Group IV	0.496	<0.001*

Table 5: Correlation between estimated GFR, urinary transferrin in general and among different groups

Correlation	Estimated GFR	
	rs	P
Urinary Transferrin	-0.542	<0.001*
Group II	-0.772	<0.001*
Group III	-0.174	0.226
Group IV	-0.537	<0.001*

Table 6: Validity (AUC, sensitivity, specificity) for urinary transferrin to discriminate between the study groups

Variable	AUC	P	95% C. I	Cut off	Sensitivity %	Specificity %	PPV %	NPV%
G I and II	0.986	<0.001*	0.970 - 1.000	2.25	88	100	100	89.3
G II and III	0.790	<0.001*	0.691 - 0.889	2.99	88	50	63.8	80.6
G III and IV	0.789	<0.001*	0.694 - 0.883	3.39	80	58	65.6	74.4

Discussion

The current study found significant high levels of urinary TF (median 7.5 ng/dl) in T2DM patients when compared to the healthy control (median 1.2 ng/dl) in agreement with Gluhovschi *et al.*, 2016 that found urine TF is elevated in normoalbuminuric individuals with T2DM, with urine ceruloplasmin and immunoglobulin G, before microalbuminuria, so designating urinary TF as a biomarker of early DN [22].

The level of urinary TF showed statistically significant differences between group III and IV (p3 value<0.001) being higher in macro than microalbuminuric patients with positive moderate correlation between urinary TF and urinary ACR in case groups (p value <0.001).

Terzić *et al.*, 2019 (study sample did not include macroalbuminuric ones) found that Urinary TF was substantially greater in the microalbuminuric individuals contrasted to in the normoalbuminuric individuals and healthy control instances and when contrasting these groups depending on the urinary TF concentration, they revealed a statistically significant positive association with urinary ACR r = 0.584 (p<0.001). [23] meanwhile Kamel *et al.*, 2022 showed that urinary transferrin was substantially greater among individuals with T2DM than in controls and significantly greater in macroalbuminuric subjects contrasted to normoalbuminuric and microalbuminuric instances owing to low molecular weight and free filtration through glomeruli. [24]

Siddiqui *et al.*, 2020 a cohort study conducted at University Diabetes Center, King Abdulaziz University Hospital, King Saud University, Saudi Arabia classified the patients according to KDIGO classification and ACR, found that urinary TF in the two classifications followed similar trend in the present work additionally revealed positive association between urinary TF with ACR (as increased protein excretion may result from glomerular hyperfiltration, insufficient tubular absorption, overflow, and/or heightened tubular secretion), exhibiting a substantial negative connection with eGFR, (since TR is less anionic compared to albumin, with an isoelectric point one unit higher). [17]

Conclusion: We can conclude that:

- Urinary transferrin (a glomerular marker) had been raised in individuals with DM, even those with a normal albumin-creatinine ratio and exhibited a positive correlation with ACR and a negative association with eGFR and is an indicator for diabetic nephropathy (DN).

Conflict of interest

There exists no conflict of interest with any financial institution concerning the content addressed in the manuscript.

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