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Urinary transferrin as early marker of renal damage in type ii diabetes mellitus: A case–control study

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ABSTRACT

Background: Microalbuminuria is a reversible stage of renal dysfunction and its detection allows early intervention and treatment of diabetic nephropathy. Therefore, a more reliable biomarker is required to diagnose early, reversible stage of renal dysfunction.
Aim: To evaluate the utility of urinary transferrin (UTRANS) as an early predictive marker in type II diabetes mellitus (T2DM).
Settings and Design: This cross-sectional study included 40 normoalbuminuric and 20 microalbuminuric T2DM patients and 20 clinically healthy controls.
Materials and methods: All baseline characteristics such as glucose (fasting and postprandial), serum creatinine, HbA1c, urinary albumin, creatinine, and UTRANS were estimated.
Statistical Analyses: SPSS software version 20, R studio 3.6.2. Shapiro test, Chi-square test, Analysis of variance, Kruskal Wallis, and receiver operating characteristic (ROC).
Results: Urinary albumin-to-creatinine ratio and UTRANS showed a significant difference among normoalbuminuric and microalbuminuric T2DM patients compared to controls ($P = 0.000$). UTRANS and TRANS/creatinine ratio positively correlated in normoalbuminuric, macroalbuminuric and control groups ($P < 0.05$). UTRANS was an excellent to outstanding discriminator (Area under the curve: 0.8 – >0.9), indicating UTRANS was able to differentiate between healthy controls, normoalbuminuric, and microalbuminuric T2DM subjects.
Conclusion: UTRANS may act as a potential biomarker that can be used as an early screening marker for renal injury, even before progression to the stage of microalbuminuria.

1. Introduction

Diabetes mellitus is a non-communicable disease that is frequently associated with the development of diabetic nephropathy, linked with a higher morbidity and mortality rate.[1] Therefore, early identification of diabetic nephropathy provides a window for treatment and may prevent worsening of the condition, which can help reduce the associated medical and economic burden.[2]

Increased level of microalbumin, ranging from 30-300 mg/24 hours urine (microalbuminuria), is a commonly used indicator for the detection of diabetic nephropathy; however, its diagnostic accuracy is limited due to the fact that renal structural damage may be ahead of albumin excretion.[3] Previous studies have confirmed that microalbuminuria is non-specific for the detection of diabetic nephropathy as even non-diabetic patients who have progressive chronic kidney disease can develop microalbuminuria.[4] Furthermore, microalbuminuric diabetic patients may not advance to end stage renal disease. Hence, there is need for specific and sensitive markers that can predict

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the susceptibility of a patient for developing diabetic nephropathy in the future. Several biomarkers have been studied so far, such as various urinary and plasma proteins (IgG, transferrin and ceruloplasmin) that are increased in cases of normoalbuminuric diabetic patients.[5–7] These biomarkers have variable degrees of diagnostic accuracy in predicting glomerular or tubular kidney damage.[8] Researchers have demonstrated a positive correlation with increasing value of HOMA-IR and reported that diabetic people have an increased level of urinary transferrin.[7] Therefore, this study aimed to evaluate the usefulness of urinary transferrin as early predictive marker in assessing renal glomerular damage in type II diabetes mellitus (T2DM).

2. Materials and Methods

2.1. Selection and description of participants

A cross sectional study was conducted from January 2016 to December 2016. Among cases, the diagnosis of diabetes mellitus was made as per the 2015 ADA Criteria.[9] Age and gender matched clinically healthy individuals with HbA1C < 5.7, FBS < 100 mg/ dl, PPBS < 140 mg/ dl or RBS < 140 mg/ dl and albumin to creatinine ratio (ACR) < 30 mg/ gm were taken as controls.[9] All cases were grouped as group 1 and group 2 based on urinary microalbumin levels. Group 1 consisted of 40 normoalbuminuric T2DM patients, whereas group 2 comprised 20 microalbuminuric T2DM patients. Pregnant women and patients admitted for surgery, patients with liver diseases, hypertension, acute infections or acute inflammatory conditions, history of any heart diseases including myocardial infarction, stroke, arteriosclerosis, history of malignancy, any disease affecting the salivary glands, trachea, stomach, colon, respiratory or genitourinary tract, complications of diabetes mellitus namely diabetic ketoacidosis, hyperosmolar coma, neuropathy and diabetic ulcers, any renal disease due to other causes, and patients on nephrotoxic drugs like aminoglycosides, amphotericin, cisplatin and those with renal transplants were excluded from this study.

2.2. Technical information

Whole blood was drawn from the median cubital vein into EDTA and gel vacutainers using aseptic precautions from each subject, at fasting and postprandial (90 minutes after meal) state. The blood was allowed to stand for clotting. Samples were centrifuged for 8 minutes at 5000 rpm and serum was collected within one hour. Glycated hemoglobin (HbA1C) was estimated immediately, and serum was used to estimate serum glucose and creatinine. Midstream urine samples were collected in sterile containers without any preservatives, followed by centrifugation for 8 minutes at 5000 rpm. Microalbumin and creatinine were estimated immediately. However, urine samples were aliquoted into sterile containers and stored at -80°C for a period of 6 months until UTRANS estimation (ELISA kit, Immunology Consultants Laboratory, E80TX Lot#9). The estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) formula: $175 \times [\text{serum creatinine (mg/dL)}]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ (if female subject)}]$.[10]

2.3. Ethics

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000. The study was approved by the institutional ethical clearance committee. All subjects were enrolled after obtaining written informed consent and were grouped into cases and controls.

2.4. Sample size

Based on a previous study,[11] it was found that the correlation between eGFR and UTRANS was –0.28 [correlation coefficient]. In the present study, the minimum sample size was calculated considering power of 80% and an alpha error of 10% to be 77. Total of 80 subjects were recruited, of whom 40 were normoalbuminuric diabetics, 20 were microalbuminuric diabetics and 20 were healthy controls.

2.5. Statistics

Data were analyzed using SPSS software version 20 and R studio 3.6.2. Shapiro test was used to check the data normalization. Normalized data, such as age, duration of diabetes mellitus and eGFR were presented as mean and standard deviation. Non-normalized data, such as levels of serum and urine creatinine, fasting blood sugar (FBS), postprandial blood sugar (PPBS), HbA_{1C}, ACR, microalbumin level, UTRANS and serum transferrin to creatinine ratio were presented as mean and standard deviation or median and interquartile range (IQR). Categorical data were presented as frequency with percentages. An association between the variables was assessed using Chi-square test. ANOVA was used to compare the means of age, duration of diabetes mellitus and eGFR among the groups. Kruskal Wallis test was used to compare the median values of eGFR, ACR, and UTRANS among the three groups. P value of <0.1 was considered as statistically significant. Correlation between eGFR, UTRANS and ACR was calculated using Spearman's correlation. A receiver operating characteristic (ROC) curve was used to determine the sensitivity, specificity, and area under ROC curve (AUC).

3. Results

The baseline characteristics of control, normoalbuminuric T2DM (group 1) and microalbuminuric T2DM (group 2) groups are presented in Table 1.

There was insignificant difference among the groups in terms of gender, age and eGFR (P >0.05). Duration of diabetes and HbA_{1C} levels also did not differ significantly between groups 1 and 2 (P >0.05).

A significant difference in the median values of FBS, PPBS, microalbumin, serum creatinine, ACR, UTRANS and serum TRANS/Creatinine ratio were noted for group 2 subjects against control group (P <0.05). Group 2 subjects also had higher values of serum creatinine, ACR, UTRANS and serum TRANS/Creatinine ratio compared to group 1 subjects (P <0.05). Group 1 subjects had significantly higher levels of FBS and PPBS compared to controls (P <0.05).

In the normoalbuminuric group (group 1), microalbumin and ACR were positively correlated (r=0.8), UTRANS correlated positively with TRANS/creatinine ratio (r=0.94) and negatively with duration of diabetic mellitus (r= -0.32). TRANS/Creatinine negatively correlated with HbA_{1C} (r= -0.35). eGFR negatively correlated with serum creatinine (r= -0.87), as shown in Table 2.

In the microalbuminuric group (group 2), microalbumin and ACR were positively correlated (r=0.81), UTRANS correlated positively with microalbumin (r=0.6), ACR (r=0.5) and TRANS/creatinine ratio (r=0.86). TRANS/Creatinine ratio positively correlated with ACR (r=0.57). eGFR negatively correlated with serum creatinine (r= -0.96), as shown in Table 3.

In the control group, ACR positively correlated with microalbumin (r=0.7) and negatively with urinary creatinine (r= -0.45). UTRANS correlated positively with TRANS/creatinine ratio (r=0.61). TRANS/Creatinine ratio negatively correlated with urinary creatinine (r= -0.72). eGFR negatively correlated with serum creatinine (r= -0.87), as shown in Table 4.

Results of Table 5 and Figure 1 show the diagnostic accuracy of UTRANS and ACR. UTRANS was an excellent to outstanding discriminator (AUC: 0.8–>0.9), indicating UTRANS was able to differentiate between controls and normoalbuminuric T2DM and microalbuminuric T2DM subjects. ACR was poorly discriminative (AUC: 0.5787) and was unable to differentiate between controls and normoalbuminuric T2DM subjects. However, ACR was an outstanding discriminator (AUC: 1.0) in distinguishing between controls and microalbuminuric T2DM subjects as well as normoalbuminuric and microalbuminuric T2DM subjects.

4. Discussion

Microalbuminuria reflects renal injury such as vascular damage, endothelial injury and inflammatory changes. In the last three decades, ACR or microalbuminuria have been considered standard diagnostic as well as prognostic biomarkers for determining the onset and progression of diabetic nephropathy.[12] However, microalbuminuria fails to specifically detect diabetic nephropathic progression where the microalbumin level exceeds the level of 300 mg/24 hours urine.[7] Microalbuminuria lacks specificity as diabetic nephropathy often progresses without any change in albumin excretion, indicating that microalbuminuria alone cannot serve as an accurate diagnostic biomarker for diabetic nephropathy.[7] The present study thus evaluated UTRANS as a biomarker in both normoalbuminuric and microalbuminuric T2DM subjects along with controls.

A gradual and significant increase in UTRANS was observed in normoalbuminuric group as compared to controls, and a further increase was noted in the microalbuminuric group when compared to normoalbuminuric group and controls (P = 0.000). Our findings concurred with the results of Al-Rubeaan et al.[7] who demonstrated that UTRANS had significant variations among the normoalbuminuric, microalbuminuric and macroalbuminuric groups as compared to controls (P <0.001). However, insignificant variations were observed within the diabetic group (groups 1 and 2) (P >0.05). The study findings were further supported by the results of Naritha et al.,[13] who showed that UTRANS excretion rates were significantly higher in diabetic patients compared to control subjects [110 (21–620) ng/minute vs. 69 (20–230) ng/minute; P <0.05]. These results support the hypothesis that UTRANS is a specific and sensitive biomarker for diagnosing diabetic nephropathy. Furthermore, UTRANS and TRANS/creatinine ratio positively correlated and eGFR and serum creatinine negatively correlated in normoalbuminuric, microalbuminuric and control groups (P <0.05).

This study also showed that the diagnostic accuracy profile of UTRANS was like that of ACR among cases of normoalbuminuric and microalbuminuric T2DM subjects with respect to AUC (0.8– >0.9). However, ACR has poor discrimination (AUC: 0.5787) and was unable to accurately differentiate between controls and normoalbuminuric T2DM subjects. As UTRANS is a urinary marker, its evaluation is more convenient and practical. A similarly excellent diagnostic accuracy profile of UTRANS in terms of AUC of 1.0 – 0.9 was shown by Al-Rubeaan et al.[7] in microalbuminuric and macroalbuminuric T2DM subjects. Conversely, UTRANS excretion had been reported in the non-diabetic population, in patients with hypertension and primary glomerulonephritis by Chelliah et al.[14] and Yaqoob et al.[15] Hence, factors such as systolic blood pressure and history of primary glomerulonephritis should be taken into consideration before using UTRANS as a biomarker to screen patients for diabetic nephropathy.

Table 1: Baseline characteristics of control, normoalbuminuric T2DM and microalbuminuric T2DM groups

Characteristics		Group 1	Group 2	Controls
Gender ¥	Male	18 (45%)	10 (50%)	12 (60%)
	Female	22 (55%)	10 (50%)	8 (40%)
Age (Years)€		49.98 ± 8.14	49.4 ± 8.97	44.95 ± 8.05
DM duration (Years)€		5.53 ± 2.81	5.15 ± 3.23	–
FBS (mg/dL)£		129 (115.5 – 170.5) ^{c}	135 (107.5 – 166.5)^{b}	90.5 (89 – 96)
PPBS (mg/dL)£		183.5 (153 – 258) ^{c}	206 (165 – 240) ^{c}	110.5 (99.5 – 124)
HbA_{1C} (%)£		7.7 (6.95 – 9.05)	8.05 (7.25 – 9.05)	–
S. Creatinine (mg/dL)£		0.69 (0.625 – 0.905)	0.84 (0.59 – 1.155) ^{a,d}	0.675 (0.53 – 0.89)
Microalbumin (mg/L)£		6.85 (3.1 – 11.1)	93.2 (41.37 – 128.95)^{c,f}	3.065 (2.075 – 3.83)
ACR (mg/g)£		5.48 (2.785 – 10.64)	111.37 (58.05 – 152.15) ^{c,f}	3.01 (2.32 – 9.8)
eGFR (mL/min)€		96.5 ± 24.44	86.5 ± 37.08 ^{a}	115 ± 34.88
UTRANS (ng/mL)£		400 (34.5 – 1240)	17380 (4570 – 25180) ^{c,f}	26 (14.5 – 43)
TRANS/Creatinine ratio (ng/mg)£		421.56 (36.99 – 1390.8)	23828 (5296.5 – 49858.7) ^{c,f}	41.21 (17.19 – 73.07)

Note: ACR: Albumin to Creatinine Ratio; DM: Diabetic Mellitus; eGRF: Estimated Glomerular Filtration Rate; FBS: Fasting Blood Sugar; Group 1: normoalbuminurics; Group 2: microalbuminurics; PPBS: Postprandial Blood Sugar; HBA1C: Glycated Hemoglobin; S: Serum; TRANS: Transferrin and UTRANS: Urinary Transferrin.

– Represents not applicable.

¥ Data were presented as frequency (%) and P-value was calculated by chi-square test; € Data were presented as mean ± standard Deviation and P-value was calculated using ANOVA; £Data were presented as median (interquartile range) and P-value was calculated using Kruskal Wallis test as the non-parametric alternative to the ANOVA.

^{a}P ≤0.05 vs. control; ^{b}P ≤0.01 vs. control; ^{c}P ≤0.001 vs. control; ^{d}P ≤0.05 vs. group 1; ^{e}P ≤0.01 vs. group 1; ^{f}P ≤.0001 vs. group 1.

Table 2: Spearman's Correlation for different variables among normoalbuminurics (Group 1)

Variables	DM Duration	FBS	PPBS	HbA1C	S. Cr	MA	U. Cr	ACR	eGFR	UTRANS	TRANS/CR
DM Duration	1	0.02	0.24	0.11	0.09	-0.07	-0.17	-0.01	-0.24	-0.32*	-0.25
FBS	0.02	1	0.64***	0.17	-0.23	-0.05	0.11	-0.23	0.23	-0.2	-0.18
PPBS	0.24	0.64***	1	0.02	-0.08	-0.13	-0.02	-0.26	0.05	-0.03	0.01
HbA1c	0.11	0.17	0.02	1	-0.15	0.02	0.23	-0.15	0.25	-0.25	-0.35*
S. Cr	0.09	-0.23	-0.08	-0.15	1	0.23	0.35*	0.27	-0.87***	0.09	-0.03
MA	-0.07	-0.05	-0.13	0.02	0.23	1	0.15	0.8***	-0.16	0.21	0.17
U. Cr	-0.17	0.11	-0.02	0.23	0.35*	0.15	1	-0.11	-0.19	-0.01	-0.31
ACR	-0.01	-0.23	-0.26	-0.15	0.27	0.8***	-0.11	1	-0.22	0.16	0.19
eGFR	-0.24	0.23	0.05	0.25	-0.87***	-0.16	-0.19	-0.22	1	0	0.08
UTRANS	-0.32*	-0.2	-0.03	-0.25	0.09	0.21	-0.01	0.16	0	1	0.94***
UTRANS/CR	-0.25	-0.18	0.01	-0.35*	-0.03	0.17	-0.31	0.19	0.08	0.94***	1
Variables	DM Duration	FBS	PPBS	HbA1C	S. Cr	MA	U. Cr	ACR	eGFR	UTRANS	TRANS/CR
DM Duration	1	0.02	0.24	0.11	0.09	-0.07	-0.17	-0.01	-0.24	-0.32*	-0.25
FBS	0.02	1	0.64***	0.17	-0.23	-0.05	0.11	-0.23	0.23	-0.2	-0.18
PPBS	0.24	0.64***	1	0.02	-0.08	-0.13	-0.02	-0.26	0.05	-0.03	0.01

Note: ACR: Albumin to Creatinine Ratio; Cr: Creatinine; DM: Diabetic Mellitus; eGRF: Estimated Glomerular Filtration Rate; FBS: Fasting Blood Sugar; HbA_{1C}: Glycated Haemoglobin; MA: Microalbumin; PPBS: Postprandial Blood Sugar; S: Serum; TRANS: Transferrin; U: Urine and UTRANS: Urinary Transferrin.

*and *** refer to <0.05 and <0.001 level of significance

Table 3: Spearman's correlation for different variables in microalbuminurics (group 2)

Variables	DM Duration	FBS	PPBS	HbA$_{1C}$	S. Cr	MA	U. Cr	ACR	eGFR	UTRANS	TRANS/CR
DM Duration	1	-0.35	-0.07	-0.15	0.33	0.26	-0.15	0.45*	-0.45*	0.02	0.19
FBS	-0.35	1	0.73***	0.37	-0.14	-0.12	-0.33	0.03	0.19	-0.03	0.09
PPBS	-0.07	0.73***	1	0.4	-0.02	-0.28	-0.48*	0.03	0	-0.19	0.08
HbA1c	-0.15	0.37	0.4	1	-0.3	-0.34	-0.23	-0.33	0.42	-0.42	-0.43
S. Cr	0.33	-0.14	-0.02	-0.3	1	0.12	0.25	0.18	-0.96***	0	0.05
MA	0.26	-0.12	-0.28	-0.34	0.12	1	0.44	0.81***	-0.2	0.6**	0.38
U. Cr	-0.15	-0.33	-0.48*	-0.23	0.25	0.44	1	0	-0.18	0.1	-0.29
ACR	0.45*	0.03	0.03	-0.33	0.18	0.81***	0	1	-0.33	0.5*	0.57**
eGFR	-0.45*	0.19	0	0.42	-0.96***	-0.2	-0.18	-0.33	1	-0.01	-0.13
UTRANS	0.02	-0.03	-0.19	-0.42	0	0.6**	0.1	0.5*	-0.01	1	0.86***
TRANS/CR	0.19	0.09	0.08	-0.43	0.05	0.38	-0.29	0.57**	-0.13	0.86***	1

Note: ACR: Albumin to Creatinine Ratio; Cr: Creatinine; DM: Diabetic Mellitus; eGRF: Estimated Glomerular Filtration Rate; FBS: Fasting Blood Sugar; HbA$_{1C}$: Glycated Haemoglobin; MA: Microalbumin; PPBS: Postprandial Blood Sugar; S: Serum; TRANS: Transferrin; U: Urine and UTRANS: Urinary Transferrin.
*, ** and *** refer to <0.05, <0.01 and <0.001 level of significance, respectively.

Table 4: Spearman's correlation for different variables in controls

Variables	FBS	PPBS	S. Cr	MA	U. Cr	ACR	eGFR	UTRANS	TRANS/CR
FBS	1	0.63**	-0.04	-0.17	-0.18	0.13	0.15	0.01	0.24
PPBS	0.63**	1	0.11	-0.3	-0.57**	0.16	-0.1	0.23	0.64**
S Cr	-0.04	0.11	1	0.22	-0.2	0.1	-0.87***	0.17	0.2
MA	-0.17	-0.3	0.22	1	0.2	0.7**	-0.24	-0.09	-0.24
U. Cr	-0.18	-0.57**	-0.2	0.2	1	-0.45*	0.21	0.05	-0.72***
ACR	0.13	0.16	0.1	0.7**	-0.45*	1	-0.16	-0.32	0.16
eGFR	0.15	-0.1	-0.87***	-0.24	0.21	-0.16	1	-0.16	-0.22
UTRANS	0.01	0.23	0.17	-0.09	0.05	-0.32	-0.16	1	0.61**
TRANS/CR	0.24	0.64**	0.2	-0.24	-0.72***	0.16	-0.22	0.61**	1

Note: ACR: Albumin to Creatinine Ratio; Cr: Creatinine; eGFR: Estimated Glomerular Filtration Rate; FBS: Fasting Blood Sugar; HbA$_{1C}$: Glycated Haemoglobin; MA: Microalbumin; PPBS: Postprandial Blood Sugar; S: Serum; TRANS: Transferrin; U: Urine and UTRANS: Urinary Transferrin.
*, ** and *** refer to <0.05, <0.01 and <0.001 level of significance, respectively

Table 5: ROC for ACR and UTRANS comparing normoalbuminurics T2DM, microalbuminurics T2DM and control groups

		ROC area	P-value	95% CI	Sensitivity	Specificity	Associated criterion
Group 1 with Control	ACR ®	0.5787	0.464	(0.42 – 0.74)	67.5%	60%	>3.6
	UTRANS	0.8144	0.0214*	(0.71 – 0.92)	67.5%	80%	>17
Group 2 with Control	ACR ®	1.00	0.381	(1.00 – 1.00)	100.0%	90%	>14.8
	UTRANS	0.985	0.426	(0.95 – 1.00)	95.0%	95%	>460
Group 2 with Group 1	ACR ®	1.00	0.439	(1.00 – 1.00)	100.0%	98%	>18.49
	UTRANS	0.94	0.126	(0.86 – 1.00)	95.0%	50%	>410

Note: ACR: Albumin to Creatinine Ratio; Group 1: normoalbuminurics; Group 2: microalbuminurics; T2DM: Type 2 Diabetes Mellitus and UTRANS: Urinary Transferrin;
® indicates ACR was taken as standard and * refers to statistically significant values of <0.05.

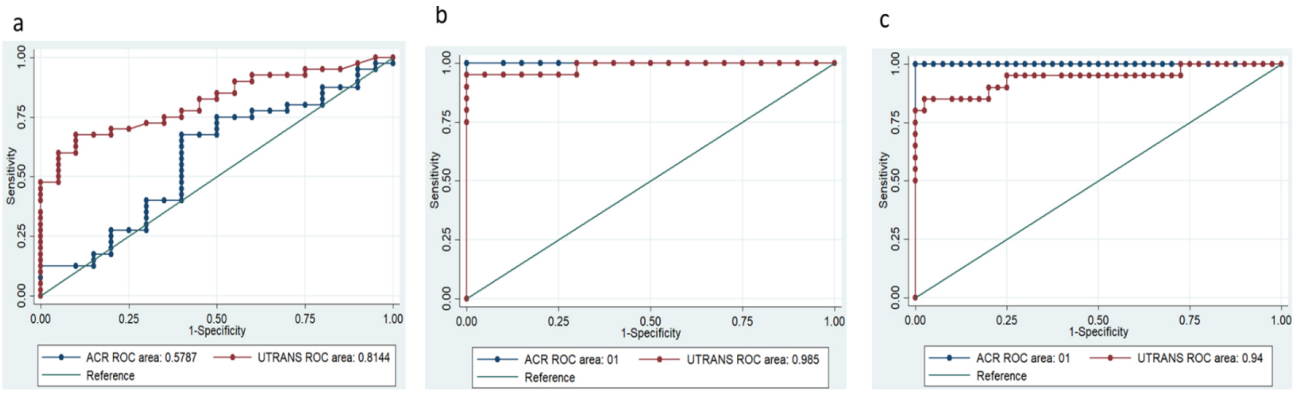

Fig. 1: Details of ROC curve **(a):** ROC for ACR andUTRANS comparing normoalbuminuric Type 2 Diabetic Mellitus with control; **(b):** ROC for ACR and UTRANS comparing microalbuminuric Type 2 Diabetic Mellitus withcontrol; and **(c):** ROC for ACR and UTRANS comparing microalbuminuric Type 2 Diabetic Mellitus with normoalbuminuric Type 2 Diabetic Mellitus
Note: ACR: Albumin toCreatinine Ratio; UTRANS: Urinary Transferrin

This study has certain limitations. First, its cross-sectional study design made it difficult to arrive at a causal relationship and demanded careful interpretation of association from the cross-sectional analysis. Second was the low sample size and the fact that subjects were non-adjusted to hypertension, which can act as a cofounding factor. Third was that other biomarkers such as urinary NGAL, interleukin and osteopontin were not considered in this study for evaluating renal injury.[7,14] Therefore, considering the above factors, a longitudinal prospective study including the above factors, with a larger sample size can be conducted to assess the predictive power of UTRANS as a reliable biomarker for diabetic nephropathy.

Conclusively, the study demonstrates that UTRANS acts as a biomarker and carries diagnostic value in the detection of early renal damage. UTRANS can detect early renal damage in normoalbuminuric and microalbuminuric T2DM subjects with significant accuracy.

5. Source of Funding

None.

6. Conflict of Interest

The authors declare that there is no conflict of interest.

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