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Diagnostic Accuracy of Urinary Neutrophil Gelatinase-Associated Lipocalin for Predicting Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus

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Abstract

Introduction: Up to 5-40% of patients with Type 2 Diabetes Mellitus develop diabetic nephropathy. For long time, microalbuminuria has been the gold standard for early diagnosis of diabetic nephropathy, but it is not a satisfactory precise predictor of DN. Thus, novel biomarkers would assist to predict DN risk. So our study aimed to determine the diagnostic role of urinary Neutrophil Gelatinase-Associated lipocalin (uNGAL) in different stages of diabetic nephropathy in comparison with albuminuria in Type 2 Diabetes Mellitus.

Materials and Methods: Prospective, case-control study, involved (100) subjects. Clinical and laboratory information was collected from all subjects during the period from August 2018 till February 2019. Subjects were divided into control group (25 healthy subjects with age and gender-matched), group 1 (25 normoalbuminuric subjects), group 2 (25 microalbuminuric subjects), and group 3 (25 macroalbuminuric subjects).

Results: uNGAL was progressively higher among the studied groups and the best cutoffs of uNGAL in the diagnosis of nephropathy in group 1, group 2, and group 3were ≥ 681ng/dl, ≥ 879.3ng/dl, and ≥ 997.8ng/dl with accuracy 96%, 92%, and 93% respectively.

Conclusion: uNGAL is superior to microalbuminuria as an early predictor of diabetic nephropathy among Type 2 Diabetes Mellitus patients and uNGAL can be used to predict and follow up the progression of diabetic nephropathy as it correlates with the severity of the disease.

Keywords: Chronic Kidney Diseases; Diabetic Nephropathy; Neutrophil Gelatinase-Associated Lipocalin; Albuminuria

Abbreviations

DN: Diabetic Nephropathy; T2DM: Type 2 Diabetes Mellitus; uNGAL: urinary Neutrophil Gelatinase-Associated Lipocalin; eGFR: estimated Glomerular Filtration Rate; DKD: Diabetic Kidney Disease; uACR: Urinary Albumin/Creatinine Ratio

Introduction

Diabetic Nephropathy (DN) represents a major health problem and affects about 20% to 40% of diabetic patients. It is one of the most significant microvascular sequelae of Diabetes Mellitus (DM) [1]. For a long time, albuminuria has been remaining as a characteristic investigation for determining diabetic nephropathy. More recently several scientists proposed that markers of tubular injury appear early in diabetic kidney disease and indeed it can occur before microalbuminuria (tubular phase) [2].

In DN, tubular hypertrophy occurs due to glucotoxicity, abnormalities of the lysosomal system, and malfunction of cubilin and megalin, which aggravate urinary protein elimination, so megalin and cubilin can be used as a diagnostic biomarker even during the normal glomerular function. Thus, researchers can utilize new biomarkers to early diagnose DN in the stage of functional damage so measures can be taken to prevent its progression [3].

Our work aimed to ascertain the diagnostic roles of urinary NGAL and urinary NGAL/urinary creatinine ratio in the different stages of diabetic nephropathy.

Materials and Methods

Study Settings and Data Collection

A prospective, case-control study was carried out in outpatient clinics of nephrology and endocrinology units of the internal medicine department in Zagazig University hospitals from August 2018 to February 2019. Informed written consent from participants and approval of institutional review board of ethical committee in the faculty of medicine, Zagazig University was done.

We included subjects with age between 30-65 years and had type 2 DM with duration 5-15 years with eGFR > 60ml/min/1.73m^2. We excluded patients with a history of uncontrolled hypertension, active infection, and inflammatory disorders or using angiotensin II receptor blockers, angiotensin-converting-enzyme inhibitors, non-steroidal anti-inflammatory drugs, nephrotoxic drugs, or immunosuppressive agents. Also, we excluded patients with coronary artery disease, stroke, peripheral vascular disease, malignancy, thyroid disorder,

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Table 1: Comparison between studied groups regarding demographic and clinical characteristics.

Demographic data	Control group	Group 1	Group 2	Group 3	Test	P
Age (years)	52.44 ± 6.23	54.08 ± 6.9	52.32 ± 7.26	56.28 ± 3.81	2.23 ª	0.09
Sex (M/F)	10/15	10/15	15/10	12/13	2.69 §	0.442
BMI (kg/m²)	26.43 ± 0.74	26.26 ± 0.75	27.28 ± 0.8	27.54 ± 0.9	14.2 ª	<0.001**(**a, b**)
SBP (mmHg)	115.2 ± 6.53	118.64 ± 11	130 ± 8.17	134 ± 8.66	26.3 ª	<0.001** (**a, b**)
DBP (mmHg)	71.6 ± 9.87	73.6 ± 11. 1	76 ± 11.9	77.2 ± 9.36	1.38 ª	0.252
Antihypertensive drugs	0 (0.00%)	6 (24%)	16 (64%)	19 (76%)	14.9 ª	<0.001** (**c**)
Lipid lowering drugs	0 (0.00%)	16 (64%)	17 (68%)	19 (76%)	0.88 ª	0.645
Diabetic retinopathy	0 (0.00%)	4 (16%)	11 (44%)	15 (60%)	10.3 ª	0.006* (**c**)
LDL (mg/dl)	72.76 ± 15.6	108.4 ± 16.8	102.7 ± 11.7	113.1 ± 9.5	43.6 ª	<0.001** (**d, e**)
HDL (mg/dl)	50 ± 6.8	36.6 ± 3.9	36.4 ± 3.44	31 ± 3.6	76.2 ª	<0.001** (**d, e**)
TC (mg/dl)	134.8 ± 23.6	187.6 ± 19.5	166.4 ± 15.8	189 ± 24.4	35.9 ª	<0.001** (**d, e**)
TGs (mg/dl)	124.8 ± 12.6	167.4 ± 46.6	156.4 ± 33.9	193.5 ± 25	19.6 ª	<0.001** (**d, e**)
HbA1c %	3.6 ± 1.31	6.65 ± 0.49	7.22 ± 0.31	7.84 ± 0.31	163 ª	<0.001** (**f**)
FBS (mg/dl)	91.6 ± 13.5	119.6 ± 12	121 ± 19.7	126.2 ± 14.7	26.1 ª	<0.001** (**f**)
Hb (g/dl)	12.6 ± 1.3	12.7 ± 1.8	11.3 ± 1.56	11.7 ± 1.29	5.29 ª	0.002* (**d, e**)
WBC's (x10³/mm³)	6.09 ± 1.7	6.57 ± 1.99	6.48 ± 1.7	6.99 ± 2.18	0.94 ª	0.424
Platelet (x10³/mm³)	265 ± 86.9	265 ± 91	289 ± 123.8	307.7 ± 99.6	26.1 ª	<0.001** (**f**)
Serum albumin (g/dl)	4.4 ± 0.35	4.24 ± 0.23	4.17 ± 0.16	3.4 ± 0.3	68.4 ª	<0.001** (**d**)
sCr (mg/dl)	0.65 ± 0.32	0.56± 0.27	0.75 ± 0.2	0.78 ± 0.23	9.32 ª	0.025* (**g**)
Urine ACR (mg/dl)	9.84 ± 7.39	12.22 ± 8.3	151.8 ± 49.6	566.8 ± 165.49	83.8 ª	<0.001** (**f**)
Serum uric acid (mg/dl)	3.62 ± 1.06	4.04 ± 0.72	4.01 ± 1.18	4.93 ± 1.58	11.8 ª	0.008* (**h**)
Blood urea (mg/dl)	16.36 ± 6.28	31.52 ± 6.3	30.62 ± 10.19	33.48 ± 7.43	42.7 ª	<0.001** (**f**)
eGFR (ml/min)	110.32 ± 36.97	115.1 ± 30.6	101.6 ± 21.33	92.56 ± 21.9	95.8 ª	0.044* (**g**)
Urine creatinine (mg/dl)	10628 ± 3052.1	12264 ± 4346	7248±820.6	6100 ± 1562.1	65.5 ª	<0.001** (**a, b**)
Urine NGAL(ng/ml)	421.4 ± 218.5	836.3 ± 45.5	942.1 ± 173.3	1173.6 ± 284	81.1 ª	<0.001** (**f**)
uNGAL/uCr(ng/mg)	0.04 ± 0.034	0.09 ± 0.09	0.13 ± 0.02	021 ± 0.08	77.8 ª	<0.001** (**a, b**)

(ª): One way ANOVA, (§): Kruskal Wallis test, (M): Male, (F): Female, (*): p ≤ 0.05 is statistically significant, (**): p ≤ 0.001 is statistically significant, (SBP): Systolic Blood Pressure, (DBP): Diastolic Blood Pressure, (BMI): Body Mass Index, (FBS): Fasting Blood Sugar, (TC): Total Cholesterol, (TGs): Triglycerides,(LDL): Low Density Lipoprotein, (HDL): High Density Lipoprotein, (HBA1c): Glycated Hemoglobin, (WBC's): White Blood Cells, (ACR): Albumin/Creatinine Ratio, (sCr): Serum Creatinine, (a): Group 3 is significantly different from group 1 and control group, (b): Group 2 is significantly different from group 1 and control group, (c): Group 1 is significantly different from group 2 and group 3, (d): Group 3 is significantly different from each other group, (e): Control group is significantly different from each other group, (f): Each group is significantly different from each other group, (g): Group 3 is significantly different from group 1, and (h): Group 3 is significantly different from the control group.

liver dysfunction, pregnant patients, or with history of non-diabetic kidney disease.

The study included 100 subjects. They were divided into:

• Control Group: It included 25 healthy subjects. They were 10 males and 15 females, and their ages range from 42-65 years with Mean ± SD 52.44± 6.23 years.

• Group 1: It included 25 type 2 diabetic patients with uACR< 30 mg/g creatinine. They were 10 males and 15 females, and their ages range from 39-65 years with Mean ± SD 54.08 ± 6.9 years.

• Group 2: It included 25 type 2 diabetic patients with uACR= 30-299 mg/g creatinine. They were 15 males and 10 females, and their ages range from 39-62 years with Mean ± SD 52 ± 7.26 years.

• Group 3: It included 25 types 2 diabetic patients with uACR ≥ 300 mg/g creatinine. They were 12 males and 13 females, and their ages range from 50 - 63 years with Mean ± SD 56.28 ± 3.81 years.

All participants in the study were exposed to the following:

1) Thorough history: A detailed history was taken with special emphasis on age, sex, history of medications, and the presence of other systemic diseases especially diabetes, hypertension, cardiovascular diseases, and previous cerebrovascular stroke.

2) Full general and local examination including blood pressure, Body Mass Index {BMI} (Quetelet's index (Kg/m²), and funds examination.

3) Laboratory investigations:

a) Routine Investigation: Peripheral venous blood samples were taken after fasting 12 hours and analyzed for lipid profile (Total Cholesterol {TC}, Triglycerides {TGs}, Low Density Lipoprotein {LDL}, and High Density Lipoprotein {HDL}) (mg/dl), serum

albumin (g/dl), glycated Hemoglobin {HbA1c%}, Fasting Blood Sugar (FBS) (mg/dl), blood urea (mg/dl) serum creatinine (mg/dl) serum uric acid (mg/dl), Complete Blood Count (CBC) and eGFR. eGFR was calculated by the modification of diet in renal disease (MDRD): 186 x (Creatinine/88.4)-1.154 x (Age)-0.203 x (0.742 if female) x (1.210 if black). Midstream urine samples were collected in the morning and analyzed for urinalysis, uACR (mg albumin/g creatinine), and urine creatinine (mg/ml). All investigations were according to methods applied in clinical pathology laboratories of Zagazig University hospitals.

b) Special investigation: urinary neutrophil gelatinase-associated lipocalin (uNGAL) in ng/dl and urinary neutrophil gelatinase-associated lipocalin to urinary creatinine ratio (uNGAL/uCr) by ELISA kit purchased from Sunred Biotechnology Company according to manufacturer's instructions. All measurements were made blind and in triplicate.

Data Analysis

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative variables were described using means and standard deviations. Categorical variables were described using their absolute frequencies and to compare the proportion of categorical data chi-square test was used. Kolmogorov-Smirnov and Levene tests were used to verify assumptions for use in parametric tests. To compare means of more than two groups, one-way ANOVA test was used when appropriate. Kruskal Wallis test was used to compare medians of more than two groups in categorical variables. Spearman correlation coefficient was used to measure the correlation between two continuous variables. ROC curve was used to determine the best cutoff of studied parameters in the diagnosis of certain health problems. The level of statistical significance was set at 5% (P<0.05). A highly significant difference was present if $p \leq 0.001$.

Results

Table (1) Comparison between studied groups regarding demographic, clinical, and laboratory characteristics.

Table (1) demonstrates the differentiation of demographic, clinical, and laboratory data among studied groups. There were no significant differences regarding age, sex, Diastolic Blood Pressure (DBP), use of lipid-lowering drugs, and White Blood Cells (WBC's). On the other hand, there were significant differences regarding BMI, systolic blood pressure (SBP), the use of antihypertensive drugs, LDL, HDL, TC, TGs, HbA1c, FBS, Hemoglobin (HB), platelets, serum albumin, serum Creatinine (sCr), uACR, serum uric acid, blood urea, eGFR, urine creatinine, uNGAL, and uNGAL/uCr. The use of antihypertensive drugs, Diabetic Retinopathy (DR), FBS, platelets, HBA1c, blood urea, urine ACR, and uNGAL were progressively higher among studied groups. Both group 2 and group 3 had higher BMI, SBP, urine creatinine, and uNGAL/uCr in comparison to the control group and group 1. Also, group 3 had higher LDL, HDL, TC, and TGs, but lower HB and serum albumin in comparison to other groups, while the opposite was true for the control group. Also, group 3 had higher sCr and lower eGFR in comparison to group 1. Furthermore, group 3 had higher serum uric acid in comparison to the control group (Figure 1).

Table (2) Correlation between urine NGAL, urine NGAL/urine creatinine, and selected study parameters

Table (2) shows that there were significant positive correlations between uNGAL and BMI, SBP, LDL, TC, TGs, HBA1c, sCr, urine ACR, serum uric acid, urine creatinine, and urine NGAL/urine creatinine. On the other hand, there were significant negative correlations between uNGAL and HDL, serum albumin, and eGFR.

Table 2: Correlation between uNGAL, uNGAL/urine creatinine, and selected study parameters.

Variable	Urine NGAL		urine NGAL/urinecreatinine	
	R	P	R	P
Age (years)	0.146	0.148	0.218	0.029*
BMI	0.405	<0.001**	0.411	<0.001**
SBP	0.605	<0.001**	0.707	<0.001**
DBP	0.191	0.057	0.286	0.004*
LDL	0.517	<0.001**	0.493	<0.001**
HDL	-0.716	<0.001**	-0.673	<0.001**
TC	0.477	<0.001**	0.404	<0.001**
TGs	0475	<0.001**	0.435	<0.001**
HbA1c %	0.833	<0.001**	0.749	<0.001**
Hb	-0.149	0.139	-0.198	0.045*
WBCs	0.182	0.070	0.199	0.047*
Platelet	0.143	0.155	0.134	0.185
Serum albumin	-0.641	<0.001**	-0.585	<0.001**
sCr	0.237	0.018*	0.241	0.016*
Urine ACR	0.821	<0.001**	0.803	<0.001**
Serum uric acid	0.297	0.003*	0.297	0.003*
eGFR	-0.216	0.031*	-0.212	0.035*
Urine creatinine	0.68	<0.001**	0.865	<0.001**
Urine NGAL	1	---	0.845	<0.001**
uNGAL/uCr	0.845	<0.001**	1	---

(*): p<0.05, statistically significant, (**): p≤0.001 is statistically highly significant, (r): Spearman Correlation Coefficient, (SBP): Systolic Blood Pressure, (DBP): Diastolic Blood Pressure, (BMI): Body Mass Index, (FBS): Fasting Blood Sugar, (TC): Total Cholesterol, (TGs): Triglycerides, (LDL): Low-Density Lipoprotein, (HDL): High-Density Lipoprotein, (HBA1c): Glycated Hemoglobin, (WBC's): White Blood Cells, (ACR): Albumin/Creatinine Ratio, and (sCr): Serum Creatinine.

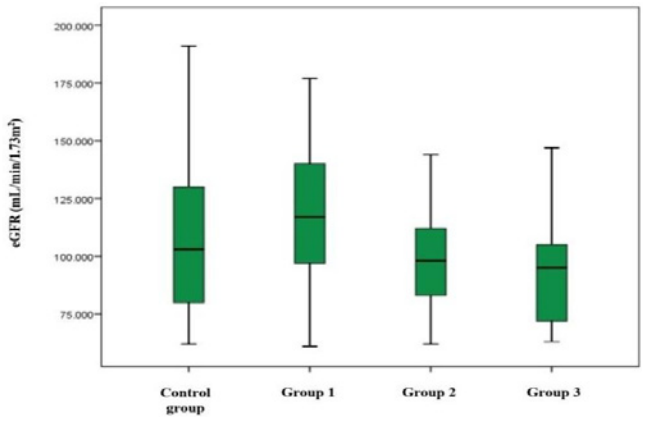

Figure 1: Boxplot showing eGFR among the studied groups.

Table 3: Performance of urine NGAL in the diagnosis of DN among studied participants.

Group	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	+LR	-LR	Accuracy	P
Group 1	≥ 681	1	100	92	92.6	100	25	0	96	<0.001**
Group 2	≥ 879.3	0.963	96	90	82.8	97.8	9.6	0.04	92	<0.001**
Group 3	≥ 997.8	0.962	96	92	80	98.6	12	0.04	93	<0.001**

Table 4: Performance of urine NGAL/urine creatinine in the diagnosis of DN among studied participants.

Group	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	+LR	-LR	Accuracy	P
Group 1	≥0.056	0.847	68	68	68	68	2.1	0.5	68	<0.001**
Group 2	≥0.097	0.978	100	86	78.1	100	7.1	0	90.7	<0.001**
Group 3	≥0.129	0.929	92	78.7	59	96.7	4.5	0.1	82	<0.001**

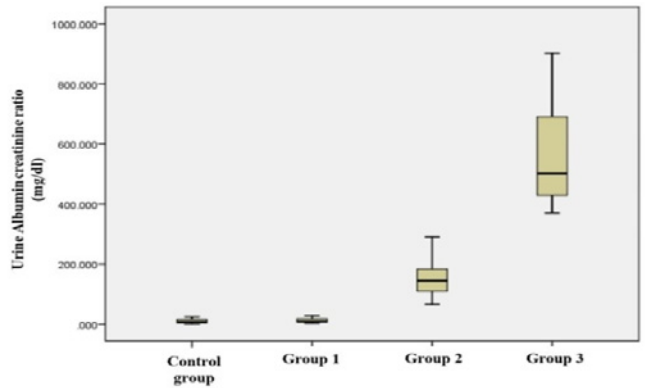

Figure 2: Boxplot showing urine albumin/creatinine ratio among the studied groups.

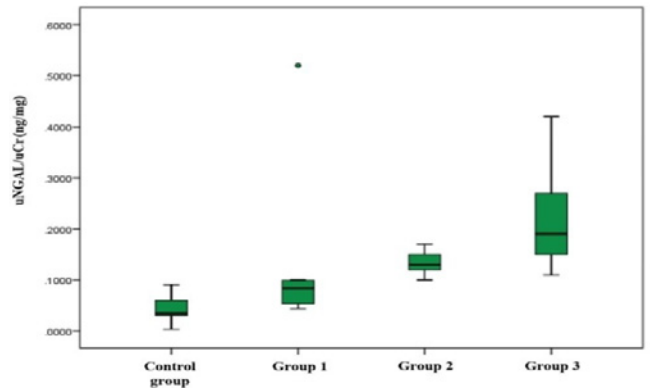

Figure 3: Boxplot showing urine NGAL/urine creatinine (uNGAL/ucr) among the studied groups.

Besides, there were significant positive correlations between urine NGAL/urine creatinine and age, BMI, SBP, DBP, LDL, TC, TGs, HBA1c, SCr, urine ACR, serum uric acid, urine creatinine, and urine NGAL. However, there were significant negative correlations between urine NGAL/urine creatinine and HDL, HB, serum albumin, and eGFR (Figure 2).

Table (3) Performance of uNGAL in the diagnosis of diabetic nephropathy among the studied participants.

Table (3) shows the best cutoffs of uNGAL in the diagnosis of nephropathy in group 1 (non-albuminuric diabetic patients), group 2 (microalbuminuric nephropathy) and group 3 (macroalbuminuric nephropathy) are ≥ 681 ng/dl, ≥ 879.3 ng/dl and ≥ 997.8 ng/dl respectively with accuracy 96%, 92%, and 93%.

Table (4) Performance of urine NGAL/urine creatinine in the diagnosis of DN among studied participants.

Table (4) shows the best cutoffs of urine NGAL/urine creatinine in the diagnosis of DN in Group 1, group 2 and group 3 are ≥ 0.056 ng/mg, ≥ 0.097 ng/mg and ≥ 0.129 ng/mg respectively with accuracy 68%, 90.7%, and 82%.

Discussion

Diabetic patients with poor glycemic control for a long time usually develop Diabetic Kidney Disease (DKD), which increases the mortality rates in those patients. It starts with expansion of the mesangial tissue, then thickening of the glomerular basement membrane and the tubular basement membrane, finally glomerular sclerosis develops. DKD usually presents with hypertension, proteinuria with reduced eGFR that leads to increased cardiovascular risk [4].

For a long time biomarkers to diagnose Chronic Kidney Disease (CKD) included elevated serum creatinine and blood urea nitrogen. On the other hand, a great decline in glomerular function occurs before a significant change in those biomarkers occurs, so they have low predictive value. Thus, there is a great need to develop new more reliable biomarkers for preliminary diagnosis of CKD. Thus, researches must be emphasized on intracellular signaling biomarkers correlated with the beginning of the process of decline of glomerular function [5].

One of these new biomarkers is NGAL that was first discovered by Kjeldsen in 1993. NGAL is a 25 kDa protein that is one of the family of the lipocalin protein [6]. In our study, we elucidated the diagnostic value of uNGAL and urine NGAL/ urine creatinine (uNGAL/uCr) in different stages of DKD in comparison with albuminuria inT2DM patients.

In our prospective case-control study, there were statistically significant differences of uNGAL and uNGAL/uCr between group 1, group 2, group 3, and control group, which indicates the importance of NGAL as a reliable marker of DKD. This is in agreement with Bolignano et al. (2009) [7] whose results showed that normo albuminuric patients had increased uNGAL levels compared with controls. uNGAL values, also in microalbuminuric patients were significantly increased compared with controls and

with normoalbuminuric subjects. Finally, patients affected by overt diabetic nephropathy showed sNGAL and uNGAL levels which were statistically higher compared with all the other groups.

Also, NGAL was progressively higher among the studied groups. That is because NGAL is one of the protective proteins against conditions with hemodynamic and metabolic dysregulation. Thus, that encourages the use of uNGAL as a predictive biomarker of the progress of DKD. In addition, there was a significant positive correlation between uNGAL and albuminuria, On the other hand, there was a significant negative correlation between uNGAL and eGFR. Those results are in agreement with Bolignano et al. (2009) [7] and Woo et al. (2012) [8]. Thus, uNGAL can be utilized as a marker to classify DKD into different stages.

In our study, there was a statistically significant difference between controls and both diabetic microalbuminuric and diabetic macroalbuminuric patients regarding uNGAL/uCr ratio. Similarly, there was a statistically significant difference between diabetic non-albuminuric patients and both diabetic microalbuminuric and diabetic macroalbuminuric patients regarding uNGAL/uCr ratio. Al-Refai et al. (2014) [9] results' were constant with ours where there was a significant difference among the control, normoalbuminuria, microalbuminuria and macroalbuminuria individuals regarding uNGAL/uCr ratio, also while the comparison of each 2 groups separately showed that there was a significant difference between the control group with each group separately. However, in contrast to our study results Al-Refai et al. (2014) [9] did not show a significant difference among the diabetic groups themselves (Figure 4).

Additionally, we evaluated the performance of uNGAL in the diagnosis of DN among the studied participants. We found that the cutoff values of non-albuminuric diabetic patients, microalbuminuric nephropathy, and macroalbuminuric nephropathy are ≥ 681 ng/dl, ≥ 879.3 ng/dl and ≥ 997.8 ng/dl respectively with diagnostic accuracy 96%, 92%, and 93%. Xiang et al. (2014) [10] who assessed the cut off values of the uNGAL in different stages of CKD found that the cut-off value of the uNGAL 82.5 mg/L for stage II, 100.5 mg/L for stage III a, 165.5 mg/L for stage III b, 254.5 mg/L for stage IV, 316.5 mg/L for stage V, respectively.

Finally, regarding uNGAL/uCr ratio, the best cutoff of uNGAL/uCr ratio in the diagnosis of early non-albuminuric nephropathy is ≥ 0.056 (ng/mg) with the area under curve 0.847, sensitivity 68%, and specificity 68%, positive predictive value 68%, and negative predictive value 68%. The best cutoff of uNGAL/uCr ratio in the diagnosis of microalbuminuria is ≥ 0.0975 (ng/mg) with the area under curve 0.978, sensitivity 100%, and specificity 86%, positive predictive value 78.1%, and negative predictive value 100%. The best cutoff of uNGAL/uCr ratio in the diagnosis of macroalbuminuria is ≥ 0.1295 (ng/mg) with the area under curve 0.978, sensitivity 92%, and specificity 78.7%, positive predictive value 59%, and negative predictive value 96.7%. Results of Kaul et al. (2018) [11] showed that uNGAL/uCr ratio had a good diagnostic profile where the best cutoff value was 24.96 ng/g, AUC of 0.996 (95% sensitivity 93.1% and specificity 100.0%, and to less extent was the diagnostic accuracy of uNGAL/uCr in the diagnosis of different stages of DKD.

Conclusion

From all the above results we can conclude that:

First, uNGAL is superior to ACR as an early predictor of DKD among T2DM patients as there was a significant difference between non-albuminuric diabetic patients and healthy individuals. Second, uNGAL and uNGAL/uCr ratio can be used to predict and follow up on the progression of DKD as they correlate with DKD severity. Third, Poor glycemic control has a significant correlation with the progression of DKD, proven by the presence of a significant positive correlation between NGAL and HbA1c. Finally, uNGAL with a cutoff value of ≥ 681.095 (ng/dl) can diagnose early non-albuminuric DN with the sensitivity of 100%, and specificity of 92 %, the positive predictive value of 92.6%, and negative predictive value of 100%.

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