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Original article

Relation Between Kidney Injury Molecule 1 (KIM 1) And Diabetic Nephropathy

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Abstract

Background: Diabetic nephropathy is a chronic disorder that takes years to develop and is characterized by a progressive rise in urinary albumin secretion. It is one of the primary consequences of diabetes mellitus. **Aim and objectives:** To investigate the relation between kidney injury molecule1 (KIM1) and diabetic nephropathy. **Patients and methods:** This was a case control research performed on 100 subjects at internal medicine department of beni-suef university hospital. Thecases were separated into 4 groups**. Results**: KIM -1 showed statistically significant varianceamongst the four studied groups with P value (<0.001) ;In Control group KIM-1 varied from 1.70 to 27.50 with mean ± SD = 12.21 ± 7.249 , In normo-albuminuric group KIM-1 ranged from 21 to 36.90 with mean ± SD = 27.11 ± 4.48 , in micro-albuminuric group KIM-1 ranged from 10.1 to 53 with mean ± SD= 42.8 ± 9.33,inmacro- albuminuric group KIM-1 ranged from.69.to 81.5 with mean ± SD = 75.5 ± 4.03. **Conclusion**:Our study

revealed increase of serum KIM 1 levels with development of Diabetic Nephropathy, reflecting the important role of Kim-1- as a biomarker for early diagnosis-and progression of DN. Serum Kim-1 is recommended to be utilized as a warning system for the development of diabetic nephropathy in people with diabetes as a screening test.

1. Introduction:

Diabetes mellitus (DM) is a significant public health concern and a chronic metabolic disorder. It is distinguished by hyperglycemia, which arises from insufficient insulin secretion or insulin resistance. While DM can impact individuals of any age, it is notably more prevalent among adults. The metabolic abnormalities that are associated with DM include the metabolism of carbohydrates, proteins, and fats (1).

One of the most prevalent diabetes complications and the primary reason for CKD is DN, a multifactorial illness (2) , activation of protein kinase C, Changes in renal hemodynamics, hexosamine biosynthesis, the aldose-reductase pathway & the formation of advanced glycation end products are some of the causes that contribute-to the decline in renal function found in cases with DN. Other explanations include: the manufacture ofadvanced-glycation end products; hexosamine biosynthesis& the production of advanced glycation end products. Other variables that contribute to this decline include advanced glycation end products. It is believed that DN affects 15%-40% of persons who have T2DM and 10%-30% of those who have T1DM (3).

Matrix metalloproteinases cleave KIM-1 at the cell surface, releasing the soluble ectodomain of KIM-1 in the urine (4), Chronic-overexpression in tubular cells causes inflammation and interstitial-fibrosis, although KIM-1 generated by acute-tubular injury provides anti-inflammatory benefits through phagocytosis (5). Further study suggests that KIM-1 in the urine might serve asa biological indicator of tubular damage.

According to recent findings, KIM-1 can be identified in the serum and has the potential to act as a biomarker for kidney injury. It was originally thought that KIM-1 emerged in the circulation following tubular injury in consequence of a loss of tubular-cell polarity and enhanced transepithelial permeability (6). However, recent research has disproved this theory(7).

The objective of our investigation was to examine the relation between KIM1 and diabetic nephropathy.

2. Patients and Methods:

This was a case control research performed on 100 subjects at internal medicine department of beni-suef university hospitalfrom February 2023 for six months. The patients were divided into 4 groups, which were as follows:Group A: 25 individuals with T2DM with normoalbuminuria. Group B: 25 individuals with T2DM with microalbuminuria. Group C: 25 individuals with T2DM with macroalbuminuria. Group D: 25 healthy individuals as control group.Diabetic Groups A,B,C : were classified according to ACR , as a standard gold test as follows : noromalbuminuria : < 30mg/gm. microalbuminuria : 30 : 300 mg/gm. macroalbuminuria: >300 mg/gm.

Inclusion criteria

Age: from 30 to 70 years old,T2DM with various degrees of DN.

Exclusion criteria

Peoples with advanced chronic liver disease, Peoples with HCV, Patients with hepatitis B, Cancer.Auto-immune diseases, Congestive heart failure.

Methods:

All patients were subjected to the following:

History taking (Personal history, Urinary incontinence,A urine that has an aberrant appearance, Excessive or insufficient production of urine, Symptoms related to obstruction, Dysuria, Uremic symptoms). Clinical examination: General (vital signs , Signs of (Cyanosis, Pallor, Jaundice & Lymph node enlargement) , Physical examination of the kidney (Serum KIM-1 levels measurement by ELISA)).

Administrative & Ethical Design

Beni-Suef University Faculty of Medicine has given their official approval for this study to proceed, Approval number; FMBSUREC/04012023/Taha , Internal medicine department at Beni-Suef University Hospital granted approval in writing, which was presented to the appropriate authorities.Approval from the ethical committee of the medical school's faculty (Institutional Research Board, or IRB). A signed consent form was collected from every patient before they were allowed to participate in the study.

Data management & Statistical Analysis

Using the statistical package of-special science SPSS version 22 (SPSS Inc. Chicago, Illinois, United States of America), all of the data was gathered, tabulated, as well as statistically analyzed in the following manner: Editing in addition to coding , Inputting of data into the computer, For parametric data, the

quantitative data were shown as mean ± SD, while for non-parametric information, the data were expressed as median & range. The qualitative information was presented in the form of frequencies and relative percentages, Shapiro-Wilk's test was utilizing to ascertain whether the data corresponded to a normal distribution. The data were processed with the use of appropriate statistical tests of significance like the following: An independent t-test in addition to a Mann–Whitney test were utilized in order to compute the variance in quantitative variables among the four groups, a comparison between two dependent groups whose variables were normally distributed was doneutilizing a paired t-test, The Chi square test ($\chi 2$) along with the fisher exact were utilized in order to calculate the differences between the qualitative variables and all statistical comparisons were conducted using two branches, with a significance threshold of p-value$\leq$ 0.05 indicating a significant, p-value below 0.001 revealing a very significant, & p-value > 0.05 indicating a variation that is not significant.

3. Results:

Table (1): Demographic characteristics among the study population

	Control group (n = 25)	Nomo-albumnuric (n = 25)	Micro-albumnuric (n = 25)	Macro-albumnuric (n = 25)	P value
Age					ANOVA 0.07
Mean ± SD.	51.68 ± 4.72	47.76 ± 3.8	49.52 ± 2.56	54.36 ± 3.77	
Median (IQR)	52 (48 - 53)	47 (45 - 51)	49 (48 - 51)	54 (52 - 57)	
Range	29 (44 - 63)	15 (42 - 57)	9 (45 - 54)	15 (47 - 62)	
Sex					0.1375
Male	15(60%)	10(40%)	13(52%)	18(72%)	
Female	10(40%)	15(60%)	12(48%)	7(28%)	
Residence					0.891
Rural	18(72%)	18(72%)	18(72%)	20(80%)	
Urban	7(28%)	7(28%)	7(28%)	5(20%)	

There was no statistically significant varianceconcerningage (p=0.07) , Sex (p=0.1375) and Residence (p=0.891) amongst the four studied groups **(Table 1).**

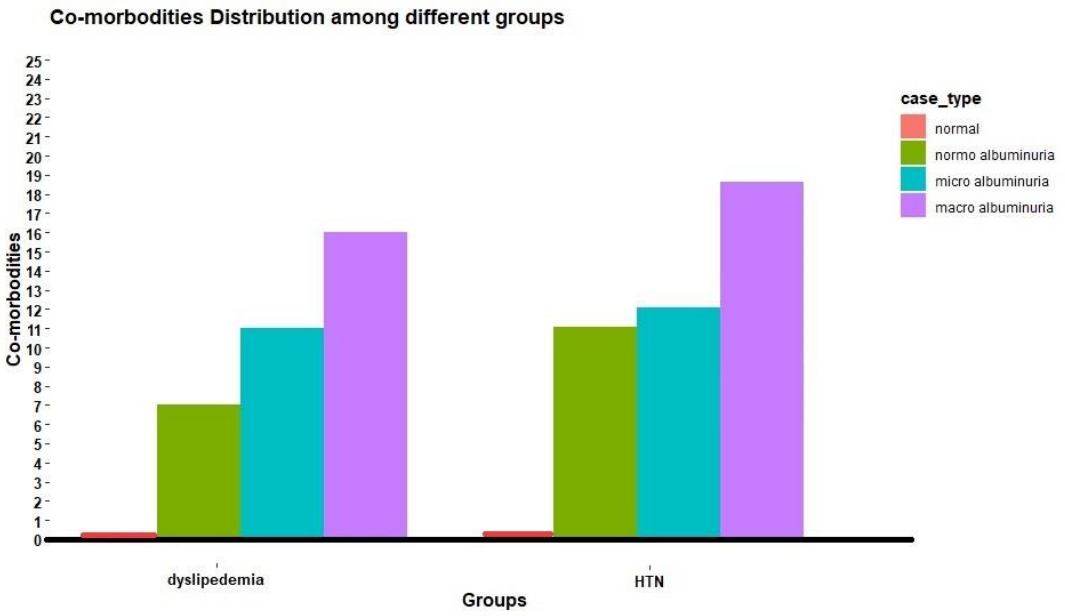

Figure (1): Bar chart illustrating comparison of research groups' Other Co-Morbidities.

Table (2): Blood glucose test results amongst the study population

	Control group (n = 25)	Nomo-albumnuric (n = 25)	Micro-albumnuric (n = 25)	Macro-albumnuric (n = 25)	P value
RBS					
Mean ± SD.	105 ± 13.6229	221 ± 15.29	239 ± 32.7	267± 35.68	<0.001
Median (IQR)	103 (96 - 110)	221(212 - 234)	237(220 – 258)	270 (235 - 300)	
Range	47(85 -132)	59(184 - 243)	165(147 - 312)	105(213 - 318)	
HbA1C					
Mean ± SD.	4.556 ± 0.605	7.312 ± 0.79	8.412 ± 0.87	10.63± 1.16	ANOVA <0.0001
Median (IQR)	4.6 (4.3- 5.1)	7.2(6.9 – 7.9)	8.6 (7.9 – 8.9)	10.3 (9.7 – 11.5)	
Range	2.1(3.4 -5.5)	2.5(6.1-8.6)	3.8(6.6 -10.4)	4.3(9.10 -13.4)	

This table showed that RBS (p=<0.001) and HbA1C (p= <.0001) showed highly statistically significant variation(p=<0.001) among the 4groups **(Table 2).**

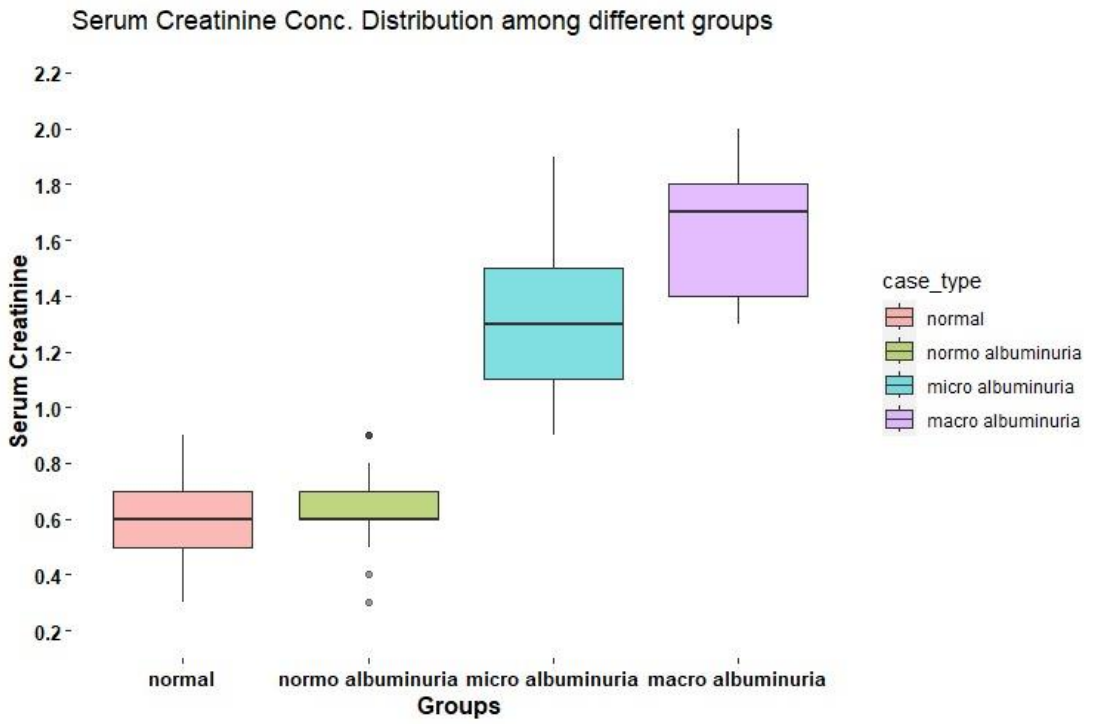

Figure (2) : A box plot demonstrating the differences in serum creatinine levels among each of the study groups.

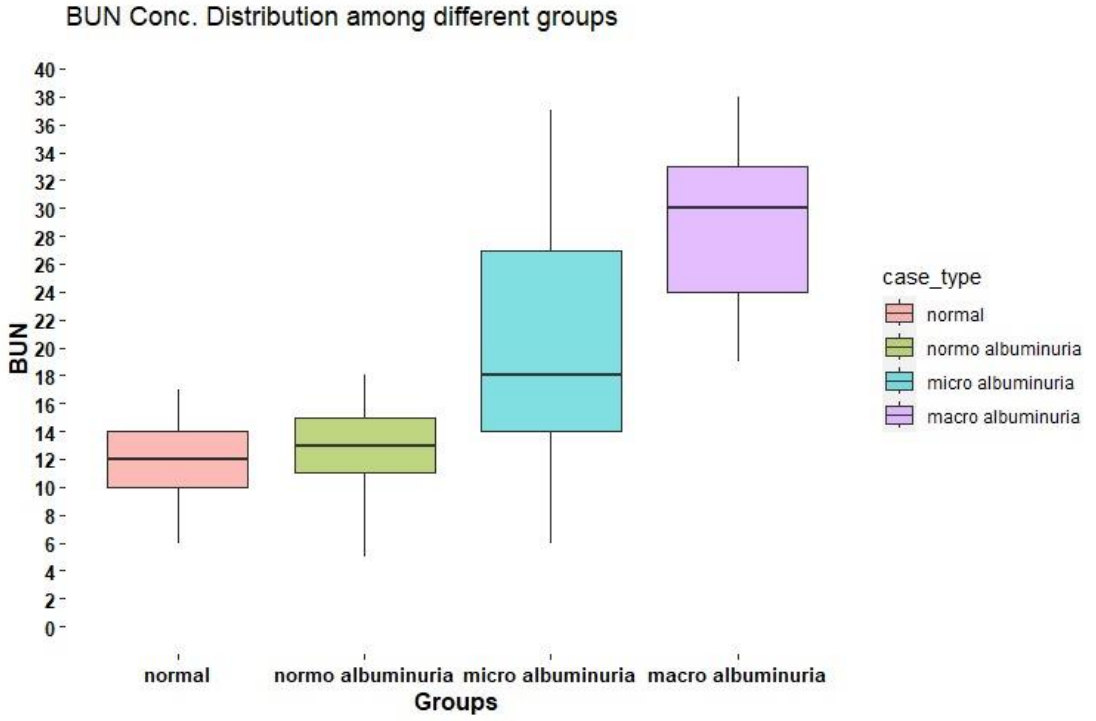

Figure (3): Box plot displaying the disparity in BUN levels among the various research groups.

Table (3): Serum KIM-1 and ACR among the study population

	Control group (n = 25)	Nomo-albumnuric (n = 25)	Micro-albumnuric (n = 25)	Macro-albumnuric (n = 25)	P value
ACR					
Mean ± SD.	5.16 ± 1.49	5.92± 1.55	185.2± 38.96	358.8 ± 47.83	<0.001
Median (IQR)	5 (4 - 6)	6 (5-7)	188 (152-209)	342 (324 - 384)	
Range (Min-Max)	5 (3- 8)	6 (3-9)	143 (113-256)	169 (309 - 478)	
KIM-1					
Mean ± SD.	12.21 ± 7.249	27.11 ± 4.48	42.8 ± 9.33	75.5 ± 4.03	<0.001
Median (IQR)	12.20 (7.30 – 17.00)	26.40 (23.30-30.10)	44.6 (37.5-49.3)	75.5 (73 – 79)	
Range (Min-Max)	25.8 (1.70– 27.50)	15.90 (21-36.90)	42.9 (10.1-53)	12.5 (69 – 81.5)	

This table showed that Albumin to Creatinine Ratio P value (<0.001) and Serum Kidney Injury Molecule -1 P value (<0.001) showed statistically significant varianceamongst the four studied groups **(Table 3).**

Table (4): Pearson's correlation coefficients (r) amongst Serum KIM-1 & other variables in diabetic cases group

Correlation with serum KIM-1		
variable	**correlations**	**p.value**
Age	0.363238	0.000204
BMI	0.87918	2.56E-33
SBP	0.886794	1.28E-34
DBP	0.854532	1.23E-29
RBS	0.76154	3.65E-20
HB A1C	0.880908	1.32E-33
Serum Creatinine	0.833353	5.62E-27
BUN	0.740835	1.24E-18
ACR	0.913858	3.83E-40
Duration of DM	0.874146	1.67E-32
eGFR	-0.82646	3.43E-26

This table showed a Strong positive relation between KIM1 and Duration of DM , ACR , serum creatinine, BUN , RBS, HBA1c, SBP ,DBP and BMI , and a strong negative relation with eGFR **(Table 4).**

Table (5) : Comparison between study groups regarding Duration of DM

	Control group (n = 25)	Normo albuminuria group (n = 25)	Micro albuminuria group (n = 25)	Macro albuminuria group (n = 25)	P value
Duration of DM (years)					**<0.001**
Mean ± SD.	**0**	**2.84 ± 1.14**	**4.48 ± 1.53**	**11.56 ± 2.99**	
Median (IQR)	**0**	**3 (2 - 4)**	**5 (3 - 5)**	**11 (9 - 13)**	
Range (Min-Max)	**0**	**4 (1 - 5)**	**5 (2 - 7)**	**13 (7 - 20)**	

Regarding duration of DM, this table showed statistically significant varianceamongst the studied groups with P value (<0.001) **(Table 5).**

Table (6) : eGFR between study groups

	Control group (n = 25)	Normo albuminuria group (n = 25)	Micro albuminuria group (n = 25)	Macro albuminuria group (n = 25)	P value
eGFR					<0.001
Mean ± SD.	103.6 ± 4.12	82.04 ± 10.51	40.2 ± 7.95	25 ± 4.96	
Median (IQR)	103(102 - 107)	84(78 - 89)	40 (35 - 47)	25 (20 - 30)	
Range (Min-Max)	17 (92 - 109)	44 (50 - 94)	26(28 - 54)	17 (18 - 35)	

Regarding eGFR**,**this table showed statistically significant variance among the four studied groups with P value(<0.001) **(Table 6).**

4. Discussion:

As regards demographic characteristics amongst the study population,Regarding Age ; there was no statistically significant varianceamongst the four studied groups (p=0.07) ;Age in control group fluctuated from 44 to 63 with a Mean ± SD 51.68 ± 4.72 , while in Normo – Albuminurinc group fluctuated from 42 to 57 with mean ± SD = 47.76 ± 3.8 , while in Micro-

Albuminuric group fluctuated from 45 to 54 with mean ± SD = 49.52 ± 2.56, while in Macro-Albuminuric group fluctuated from 47 to 62 with mean ± SD= 54.36 ±3.77 ,Regarding sex : there was no statistically significant variancebetween the fourstudiedgroups (p=0.1375) ,Concerning Residence: there was no statistically significant varianceamongst the fourstudiedgroups(p=0.891).

The present study was in agreement withBalu et al., (8). With the objective of examining the efficacy of serum KIM-1 as a prognostic indicator of DN. The mean age and gender of the groups did not differ significantly (P = 0.26, 0.339), the researchers discovered.As regards Clinical characteristics amongst the study population;Regarding Other Co-Morbidities: there was significant variance among the four studied groups regarding other comorbidities (Dyslipidemia and HTN) with P.Value(<0.0001).BMI ; also varied statistically with P Value (<0.001) : in control group BMI ranged from 19.7 to 23 with Mean±SD= 21.2±1.04 , in Normo-albuminuric cases BMI ranged from 19.5 to 23.1 with mean ± SD = 21.65 ± 1.046, in Micro-albuminuric cases BMI ranged from 24.6 to 26.8 with mean ± SD = 25.66 ± 0.6225 , in Macro-albuminuric cases BMI ranged from 26 to 30.4 with mean ± SD = 27.33 ± 1.004.

This study can be supported by Khan et al.,(9) They found that there was statistically significant varianceconcerning BMI amongst the groups (p=0.003).

Regarding Blood glucose test results among the study population;. Regarding Random Blood Sugar ; RBS showed highly statistically significant variation (p= <0.001) among the 4 groups; In Control group the RBS varied from 85 to 132 with mean ± SD = 105 ± 13.6229 , in Normo-albuminuric cases group RBS varied from 184 to 243 with mean ± SD = 221 ± 15.29 , in Micro-albuminuric cases group RBS varied from 147 to 312 with mean ± SD = 239 ± 32.7 , in Macro-albuminuric cases group RBS varied from 213 to 318 with mean ± SD = 267± 35.68 . Regarding HbA1C : it showed highly statistically significant variations (p= <.0001) among the 4 groups ; In Control group ; the HbA1C varied from 3.4 to 5.5 with mean ± SD = 4.556 ± 0.605 , In Normo-albuminuric cases group ; HbA1C ranged from 6.1 to 8.6 with mean ± SD = 7.312 ± 0.79 , in Micro-albuminuric cases group ; HbA1C ranged from 6.6 to 10.4 with mean ± SD = 8.412 ± 0.87, in Macro-albuminuric cases group ; HbA1C ranged from9.10to13.4.with.mean±SD=10.63±1.16.

The current investigation corroborated the findings of Quang et al. (10). In order to assess the early diagnostic utility of two tubular-specific markers—KIM-1 and neutrophil gelatinase-associated lipocalin (NGAL)—diabetes nephropathy was the focus of this investigation. No statistically significant distinctions were observed in FPG and HbA1c levels between two groups of diabetes cases.

Regarding Kidney function test results among the study population. Regarding Serum Creatinine ; there was statistically significant variance among the four studied groups with P value (>0.001) ; in Control group the Serum Creatinine varied from 0.3 to 0.9 with mean ± SD = 0.572 ± 0.145 , in Normo-albuminuric cases group it varied from 0,3 to 0.9 with mean ± SD = 0.65 ± 0.153 , in Micro-albuminuric cases group it varied from 0.9 to 1.9 with mean ± SD = 11.336 ± 0.3025, in Macro-albuminuric cases group it ranged from 1.3 to 2 with mean±SD=1.632±0.217, Also regarding BUN ; there was statistically significant variance among the four studied groups with P value (>0.0001) ; in Control group the BUN varied from 6 to 17 with mean ± SD = 11.64 ± 3.3 , in Normo-albuminuric cases group it varied from 5 to 18 with mean ± SD = 13.32 ± 3.07, in Micro-albuminuric cases group it varied from 6 to 37 with mean ± SD = 20.12 ± 9.01 , in Macro-albuminuric cases group it varied from 19 to 38 with mean ± SD = 29.24 ± 0.126.

Consistent findings were found between the current study and Balu et al. (9). Researchers discovered that those with diabetes and microalbuminuria had greater serum creatinine levels than those without diabetes and microalbuminuria (P = 0.020) while people in the control group had lower serum creatinine levels than those with diabetes and microalbuminuria (P = 0.001). However, serum creatinine levels did not differ significantly among the healthy controls and the diabetics who did not have microalbuminuria (P = 0.28). Serum KIM-1 levels were significantly a distinct amongst those without diabetes and those with it (P= 0.0001). It was also shown that there was a statistically significant distinction (P = 0.001) between the two groups (control and diabetes with microalbuminuria). When comparing diabetic individuals with and without microalbuminuria, however, there was no significant distinction in serum KIM-1 (P = 0.99).

Regarding durationof DMin different study groups: It showed statistically significant variance among the studied groups with P value (<0.001) ; Duration of DM in Normo albuminuria group varied from 1 to 5 with mean ± SD = 2.84 ± 1.14 , while in Micro albuminuria group

varied from 2 to 7 with mean ± SD = 4.48 ± 1.53 , while in Macro albuminuria group varied from 7 to 20 with mean ± SD = 11.56 ± 2.99 , while none of control groupwasdiabetic.

Ahmed et al. (11) found similar results, which were confirmed by the current investigation. With the goal of enhancing early diagnosis, predicting disease progression, and delivering new insights into the pathogenic basis of diabetic nephropathy, researchers set out to ascertain the promising diagnostic significance of kidney injury molecule-1 (KIM-1) level and 2 microglobulin. When comparing the duration of diabetes in the macroalbuminuric group to that of the normoalbuminuric and microalbuminuric groups, they discovered a statistically significant distinction.In our study Pearson's correlation coefficients (r) between Serum KIM-1 and other variable we found that there is aStrong positive relation between KIM1 and Duration of DM, ACR, serum creatinine, BUN, RBS, HBA1c, SBP, DBP BMI and eGFR.

This study can be supported byAslan et al.(12). They found that Spearman's correlation analysis revealed a positive relationship among KIM-1 and both urine microalbumin and urine microalbumin/creatinine (r=0.479, P<0.001,r=0. 400, P<0.001; respectively).

5. Conclusion:

Our study revealed increase of serum KIM 1 levels with progression of Diabetic Nephropathy, reflecting the important role of Kim-1 as a biomarker for early diagnosis and progression of DN. Serum Kim-1 is recommended for use as a warning system for the development of diabetic nephropathy in individuals with diabetes as a screening test.

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