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# URINARY TYPE IV COLLAGEN: CAN IT BE USED AS AN INDICATOR FOR THE PROGRESSION OF DIABETIC NEPHROPATHY?

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***Keywords:*** *Nephropathy, Diabetic, Urinary etc.*

## *Abstract*

Introduction: Diabetic nephropathy is a complication seen in long standing diabetes mellitus where progressing impairment of kidney function leads to end-stage renal disease. In the advanced diabetic nephropathy, immunoreactive type IV collagen was detected in glomerular basement membrane (GBM), tubular basement membrane and Bowman's capsule much more than that in the normal kidney. However, there is little information on whether the increase in type IV collagen excretion in urine is a predictor of progression of diabetic nephropathy or deterioration of renal function in type 2 diabetic patients. We conducted this work with the aim to determine whether the urinary levels of type IV collagen can predict the progression of diabetic kidney disease in Type 2 DM.

Subjects and Methods: This study included 100 adult patients; who were classified into: 20 diabetic normoalbuminuric patients (group1),20 diabetic microalbuminuric patients(group2), 20 diabetic macroalbuminuric(group3),20 diabetic CKD patients with GFR:60-90ml/min(group4), 20 diabetic CKD patients with GFR:30-59ml/min(group5), and compared with 20 controls (group6) . All included subjects were subjected to renal function test and estimated creatinine clearance by Modification of Diet in Renal Disease (MDRD) formula. Measurements of urine albumin/creatinine ratio. Fasting blood glucose and hemoglobin A1C.The urinary concentrations of type IV collagen were measured using a highly sensitive one-step sandwich enzyme immunoassay kit.

Results: Urinary type IV collagen was significantly higher in normoalbuminuric patients than the control group, in microalbuminuric patients than both control and normoalbuminuric, , in macroalbuminuric than normo and micro albuminuric and control , in CKD1, CKD2 groups it was significantly higher than all other groups and highest in CKD2..

Conclusions: Urinary type IV collagen can be used as an early marker for the development of DN and as an indicator for the progression of the disease.

## INTRODUCTION

Diabetic nephropathy is a complication seen in long standing diabetes mellitus where progressing impairment of kidney function leads to end-stage renal disease (ESRD). It affects both type 1 and type 2 diabetes patients and is the most common kidney condition requiring dialysis. (1)

Proteinuria is generally regarded as a marker for the degree of glomerular damage, the level of proteinuria correlates well with the prognosis for renal function, and interventions that retard the progression of diabetic renal disease also reduce proteinuria. However, it is not yet know whether the flux of protein across the glomerular basement membrane is causally implicated in the evolution of diabetic renal disease or simply reflects glomerular damage. (2)

Detection of diabetic nephropathy as early as possible in the disease process currently offers the best chance of delaying or possibly preventing progression to end-stage disease. Therefore, screening for microalbuminuria and proteinuria in a structured, regular manner is recommended. (3) So the need for new screening methods has emerged, one of these methods is type IVcollagen.

Current models depict the basic structure of the basement membrane as a three-dimensional network of type IV collagen. (4)

Type IV collagen is the antigenic target in Goodpasture's disease , and mutations in the genes of the α3, α4, and α5 chains of type IV collagen are responsible for Alport's syndrome.(5-7)

Diabetic nephropathy is characterized structurally by accumulation of mesangial matrix and thickening of the basement membrane in the glomeruli, (8) as well as renal tubular hypertrophy and associated basement membrane alterations in the tubulointerstitium, which precede tubulointerstitial fibrosis.(9) These abnormalities are associated with renal overproduction of the extracellular matrix proteins such as type IV collagen. (10) The production of type IVcollagen is enhanced in glomerular mesangial cells,(11) podocytes(12), and proximal tubular cells cultured under a high-glucose condition. (13)

In the advanced diabetic nephropathy, immunoreactive type IV collagen was detected in glomerular basement membrane (GBM), tubular basement membrane and Bowman's capsule much more than that in the normal kidney. (14)

## PATIENTS & METHODS

This study included 100 patients with type 2 diabetes mellitus, from the internal medicine department, faculty of medicine, university of Alexandria, who were divided into 5 groups:
**Group I:** Included 20 patients with normoalbuminuria and normal GFR.
**Group II:** Included 20 patients with microalbuminuria and normal or raised GFR.
**Group III:** Included 20 patients with macroalbuminuria and normal or raised GFR.
**Group IV:** Included 20 chronic kidney disease (CKD) diabetic patients with eGFR: 60-90 ml/min.
**Group V:** Included 20 CKD diabetic patients with eGFR: 30-59 ml/min.

The control group consists of 20 healthy volunteers who are neither diabetic nor hypertensive and not complaining of any renal problem. (**Group VI)**

Patients with Hypertension, Systemic lupus erythematosis, another kidney disease, Hepatic disease including HCV were excluded

The study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and an informed consent was obtained from each patient.

- All included subjects were subjected to: Renal function test: blood urea, serum creatinine and estimated creatinine clearance by Modification of Diet in Renal Disease (MDRD) formula. [15]

- Complete urine analysis with measurement urine albumin/creatinine ratio. [15]

- Fasting blood glucose and hemoglobin $A_{1C}$. [16]

- The urinary concentrations of type IV collagen were measured using a highly sensitive one-step sandwich enzyme immunoassay kit.This assay used two monoclonal antibodies against the 7S domain and the triple helix domain of human placental type IV collagen .The procedure was performed according to the instruction provided by the manufacturer. The urinary concentrations of creatinine were simultaneously measured by the Jaffe method. The urinary excretion levels of type IV collagen were expressed as micrograms per gram of creatinine.[17]

- Complete lipid profile: cholesterol, triglycerides, high density lipoproteins (HDL), low density lipoproteins (LDL). [15]

**Statistical Methods:** Data were fed to the computer using IBM SPSS software package version 20.

Qualitative data were described using number and percent. Comparison between different groups regarding categorical variables was tested using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Firsher's Exact test or Monte Carlo correction.

The distributions of quantitative variables were tested for normality using Shapiro-Wilk test and D'Agstino test, also Histogram and QQ plot were used for vision test. If it reveals normal data distribution, parametric tests was applied. If the data were abnormally distributed, non-parametric tests were used.

Quantitative data were described using mean and standard deviation for normally distributed data while abnormally distributed data was expressed using median, minimum and maximum.

For normally distributed data, comparison between different groups were analyzed using F-test (ANOVA) and Post Hoc test (Scheffe) for pair wise comparison, while for abnormally distributed data, Correlations between two quantitative variables were assessed using Pearson coefficient. Kruskal Wallis test was used to compare between different groups and pair wise comparison was assessed using Mann-Whitney test. Correlations between two quantitative variables were assessed using Spearman coefficient.

Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level. (Statistical significant was considered at $p \leq 0.05$)

## RESULTS

There was a significant difference regarding the duration of diabetes among the studied groups. **(Table 1)**

Regarding glycemic control, there was significant difference between all the studied groups and the control as regards the HbA1C. There was significant difference between the macroalbuminuric, CKD1, CKD2 groups and the normoalbuminuric group as regards the HbA1CThere was significant difference between the CKD2 group and the microalbuminuric group as regards the HbA1C. Otherwise there was no significant difference regarding the rest of the groups. ($P<0.05$) **(Table 2)**

Regarding eGFR, There was no significant difference regarding the eGFR between the normoalbuminuric, microalbuminuric, macroalbuminuric group in relation to each other and in relation to the control.( $P< 0.05$)

While there was a significant difference regarding MDRD in CKD1and CKD2 groups when compared to each other and to other groups. ( $P<0.001$). **(Table3)**

There was a significant difference between the studied groups regarding lipid profile. **(Table 4)**

Regarding urinary excretion of type IV collagen, there was significant difference between the normoalbuminuric, microalbuminuric, macroalbuminuric, CKD1, CKD2 groups and the control as regards the U4col. There was significant difference between the microalbuminuric, macroalbuminuric, CKD1, CKD2 groups and the normoalbuminuric as regards the U4col. There was significant difference between the macroalbuminuric, CKD1, CKD2 groups and the microalbuminuric as regards the U4col. There was significant difference between the CKD1, CKD2 groups and the macroalbuminuric as regards the U4col. There was significant difference between the CKD1 group and the CKD2 groups as regards the U4col. **(Figure 1)**

There was a statistically significant positive correlation between **U4C** and duration of diabetes, HbA1c, ACR, triglycerides and LDL. **(Figures 2-4)**

There was a negative correlation between **U4C** and MDRD and HDL**.( Figure5)**

## DISCUSSION

Diabetic nephropathy occurs in approximately one-third of all people with diabetes and is the leading cause of renal failure in developed and developing countries. [18]

Although microalbuminuria in diabetic patients is considered to be the best predictor of progression to End-Stage Renal disease and cardiovascular events earlier, more sensitive and specific markers of kidney damage might help to diagnose and treat diabetic nephropathy at an earlier stage to prevent the progression to renal failure.[19]

Multiple biomarkers in serum and urine have been studied that represent di erent mechanisms or structural damage, based on which they have been classified as markers of glomerular injury, tubular injury, oxidative stress, inflammation, and endothelial damage. [20,21]

Urinary markers of glomerular damage represent either, increased permeability to plasma proteins (albumin; transferrin), or increased excretion of extracellular matrix proteins (type IV collagen; fibronectin) The former is secondary to three mainfactors: loss of glomerular charge selectivity,loss of glomerular size selectivity,or increased intraglomerular pressure.[22]

Type IV collagen is the major collagenous component of the extracellular matrix (ECM). It is generally considered that the accumulation of ECM including type IV collagen, fibronectin and laminin, leads to glomerular sclerosis in various renal diseases.The increase of urinary type IV collagen concentration in diabetic patients might be reflected by the increase of its production and/or decrease in its degradation. . [23]

This study showed that there was a decline in the renal function regarding the level of the B.urea and the S.creatinine,at later stages of the disease(CKD1,CKD2) compared to the control, and there was no decline in the normoalbuminuric, microalbuminuric, and the macroalbuminuric stages. This means that we can't depend on urea and creatinine measurements only to detect renal injury, and that the disease may be progressing from one stage to another without significant decline in the renal functions.

This finding was agreed by Shemesh O et al[24], who said that Long term studies on the prognostic implications of markers rather than blood urea and serum creatinine need to be conducted.

This study showed that there was no significant difference between the normoalbuminuric group and the control regarding 24 h urinary proteins and ACR, but there was significant difference between both groups regarding type IV collagen excretion. Based on these results, it was proposed that urinary type IV collagen could increase before any increase in albuminuria in diabetic patients and could be a useful marker for the identification of early stages of diabetic nephropathy.

This finding was agreed by many investigators [25-27] who proposed that urinary type IV collagen could increase before any increase in albuminuria in diabetic patients.

This study showed that there was no significant difference between the normoalbuminuric, microalbuminuric, macroalbuminuric groups and the control regarding creatinine clearance by MDRD equation, which means that the patient may be developing progressive renal injury without significant reduction in the e GFR this also highlights the importance of discovering new markers to detect DN,and its progression in different disease stages.

This finding was agreed by other authors [28,29] who have seen that GFR estimations based upon MDRD equation is unacceptable for monitoring kidney function in type 2 diabetic patients with incipient and overt diabetic nephropathy.

The main findings in our study were that the excretion of urinary type 4 collagen was significantly increased in diabetic patients compared to the control and the five diabetic groups showed progressive increase in the level of urinary 4 collagen ranging from (0.66 ± 0.12µg/g of creatinine) in normoalbuminuric group till it reached (3.40 ± 0.78) in CKD patients with eGFR 30-59 ml/min and there was a significant correlation between albumin excretion and collagen excretion ($p < 0.001^*$).

Yagame et al [30] had reported a similar observation. In their study, they noted that type IV collagen excretion increased in accordance with the increase in urine albumin excretion.

The present study has shown that the excretion of urinary type IV collagen started in diabetic patients even with normoalbuminuria, even before albuminuria begin to appear.

This result was supported by other studies as Kotajima N et al [31] and Pavai et al.[23] who noted that higher levels of urinary type IV collagen had also been reported even in normoalbuminuric individuals than that of controls.

The concentration of urinary type IV collagen in normoalbuminuric group patients was higher (0.66 ± 0.12µg/g of creatinine) than normal controls (0.24 ± 0.03 µg/g of creatinine).

In a follow-up study of 94 diabetic patients, Tomino et al.[32] found that after 1year , 25% of normoalbuminuric patients with increased urinary type IV collagen excretion developed microalbuminuria ,and 75 % stayed normoalbuminuric. The patients that stayed normoalbuminuric had a significant decrease in the urinary type IV collagen excretion, while the patients that developed microalbuminuria had a further increase in type IV collagen excretion, Tomino et al. showed that the urinary excretion of type IV collagen in diabetic patients increased gradually as renal diseases progressed.

Mogensen [33] reported that 80% of patients with type 1 diabetes mellitus and 20% of patients with type 2 diabetes mellitus with microalbuminuria develop overt proteinuria in 10 years.

The present study have shown that there was statistically significant correlation between the urinary type IV collagen excretion and the duration of diabetes ($p<0.001$) This results was supported by other studies as they reported that urinary type IV collagen excretion in type 2 diabetic patients is significantly associated with the duration of diabetes[21]

The present study observed that urinary type IV collagen levels were inversely correlated with creatinine clearance ($r= -0.846^*$ and $p<0.001$) this finding is in agreement with those reported by Cohen et al. [34] who measured the urinary excretion of (human) collagen IV by immunoassay in 65 patients with type 1 or type 2 diabetes and various degrees of albuminuria, observed a negative correlation between collagen excretion and creatinine clearance.

Such a relationship suggests that renal function in patients with high collagen excretion might be deteriorating gradually.

The present study have shown that there was Statistically significant correlation between level of urinary type IV collagen and level of HbA1C ($p<0.001$) This finding is in agreement with Haneda et al[11] who showed that glucose enhances type IV collagen production in cultured rat glomerular mesangial cells. Increased serum type IV collagen concentrations have been observed in patients with increased blood glucose levels. These data suggest that a significant relationship should exist between glycaemic control (HbA1C) and concentration of urinary type IV collagen. [32]

Additionally, this study observed that urinary type IV collagen levels were inversely correlated with serum HDL cholesterol levels ($r = -0.310^{*}$and $p=0.005$) Wada et al. [35] observed the same results.

On the other hand , this study observed that urinary type IV collagen levels were positively correlated with serum LDL cholesterol levels ($r= 0.554^{*}$,$P<0.001$) .Demetrius Ellis et al, a10 years follow-up study of childhood-onset Type I diabetes of 62 diabetic patients, observed the same result. This was explained by the fact that low density lipoprotein (LDL) stimulates the production of extracellular matrix by mesangial cells. [35]

Although microalbuminuria is the established predictor of risk for subsequent development of diabetic nephropathy, not all patients with microalbuminuria progress to overt nephropathy.

This discrepancy is particularly notable in type 2 diabetes mellitus.

In present study, type 2 diabetes mellitus patients have increased levels of urinary type IV collagen.

Excretion of urinary type IV collagen may be a useful indicator of early diabetic nephropathy and a useful predictor for the progression of diabetic nephropathy as well.

Furthermore, the ratio of urinary type IV collagen to albumin may be useful for differential diagnosis between early diabetic nephropathy and progressive glomerular nephritis.[21]

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## FIGURES AND TABLES LEGENDS

***Table (1): Comparison between the different studied groups according to diabetes duration***

| | Normo | Micro | Macro | CKD | | Control | Test of sig. |
|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | | |
| **Duration** | | | | | | | |
| Min. – Max. | 1.0 – 6.0 | 10.0 – 20.0 | 17.0 – 24.0 | 21.0 – 26.0 | 23.0 – 33.0 | - | |
| Mean ± SD | 3.55 ± 1.70 | 13.45 ± 2.82 | 19.90 ± 2.22 | 23.70 ± 1.77 | 27.40 ± 3.13 | - | $^{F}p<0.001^{*}$ |
| Median | 3.50 | 13.0 | 19.50 | 23.50 | 27.0 | - | |
| $^{Sch}p_2$ | | <0.001* | <0.001* | <0.001* | <0.001* | | |
| $^{Sch}p_3$ | | | <0.001* | <0.001* | <0.001* | | |
| $^{Sch}p_4$ | | | | 0.003* | <0.001* | | |
| $^{Sch}p_5$ | | | | 0.021* | | | |

***Table (2): Comparison between the studied groups according to HBAIC***

| | Normo | Micro | Macro | CKD | | Control | p |
|---|---|---|---|---|---|---|---|
| **HBAIC** | | | | 1 | 2 | | |
| Min. –Max. | 7.0 – 8.20 | 7.20 – 8.80 | 7.40 – 8.70 | 7.0 – 9.10 | 7.50 – 9.50 | 4.60 – 5.80 | |
| Mean ± SD | 7.58 ± 0.40 | 7.90 ± 0.47 | 8.08 ± 0.41 | 8.44 ± 0.64 | 8.52 ± 0.61 | 5.07 ± 0.41 | <0.001* |
| Median | 7.50 | 7.85 | 8.05 | 8.55 | 8.50 | 4.95 | |
| $p_1$ | <0.001* | <0.001* | <0.001* | <0.001* | <0.001* | | |
| $p_2$ | | 0.442 | 0.048* | 0.001* | <0.001* | | |
| $p_3$ | | | 0.913 | 0.124 | 0.047* | | |
| $p_4$ | | | | 0.558 | 0.324 | | |
| $p_5$ | | | | 1.000 | | | |

***Table (3): Comparison between the studied groups according to MDRD***

| | Normo | Micro | Macro | CKD | | Control | p |
|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | | |
| **MDRD** | | | | | | | |
| Min. –Max. | 98.0 – 124.0 | 91.0 – 122.0 | 90.0 – 110.0 | 62.0 – 83.0 | 30.0 – 52.0 | 90.0 – 120.0 | |
| Mean ± SD | 114.65 ± 8.16 | 106.8 ± 11.56 | 98.8 ± 5.40 | 72.2 ± 7.38 | 40.8 ± 7.55 | 107.0 ± 11.04 | <0.001* |
| Median | 117.50 | 105.50 | 96.50 | 72.50 | 40.50 | 103.0 | |
| $p_1$ | 0.222 | 1.000 | 0.089 | <0.001* | <0.001* | | |
| $p_2$ | | 0.196 | 0.052 | <0.001* | <0.001* | | |
| $p_3$ | | | 0.104 | <0.001* | <0.001* | | |
| $p_4$ | | | | <0.001* | <0.001* | | |
| $p_5$ | | | | <0.001* | | | |

***Table (4): Comparison between the studied groups according to lipid profile***

p: p value for comparing between the studied groups
$p_1$: p value for comparing between control and each other group
$p_2$: p value for comparing between normo and micro, macro, CKD4 and CKD5
$p_3$: p value for comparing between micro and macro, CKD4 and CKD5
$p_4$: p value for comparing between macro and CKD
$p_5$: p value for comparing between CKD4 and CKD5
FE: Fisher Exact test
KW: Kruskal Wallis test
Sch: Post Hoc Test (Scheff)
MW: Mann Whitney test
*: Statistically significant at $p \leq 0.05$

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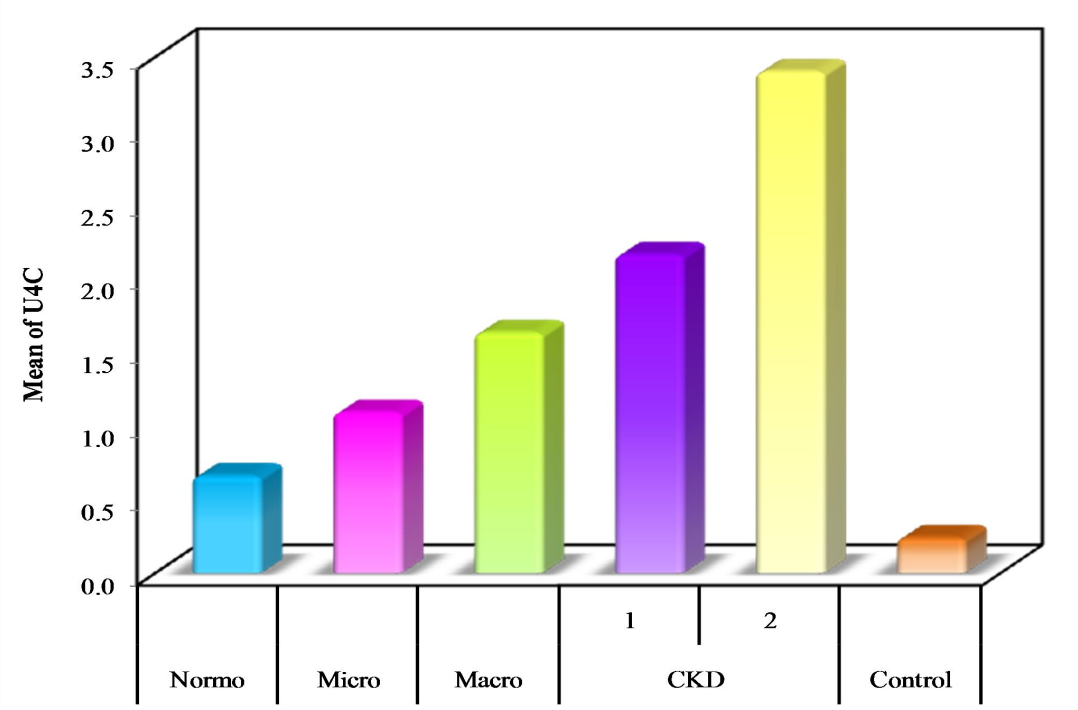


*Figure (1): Comparison between the studied groups according to U4C*

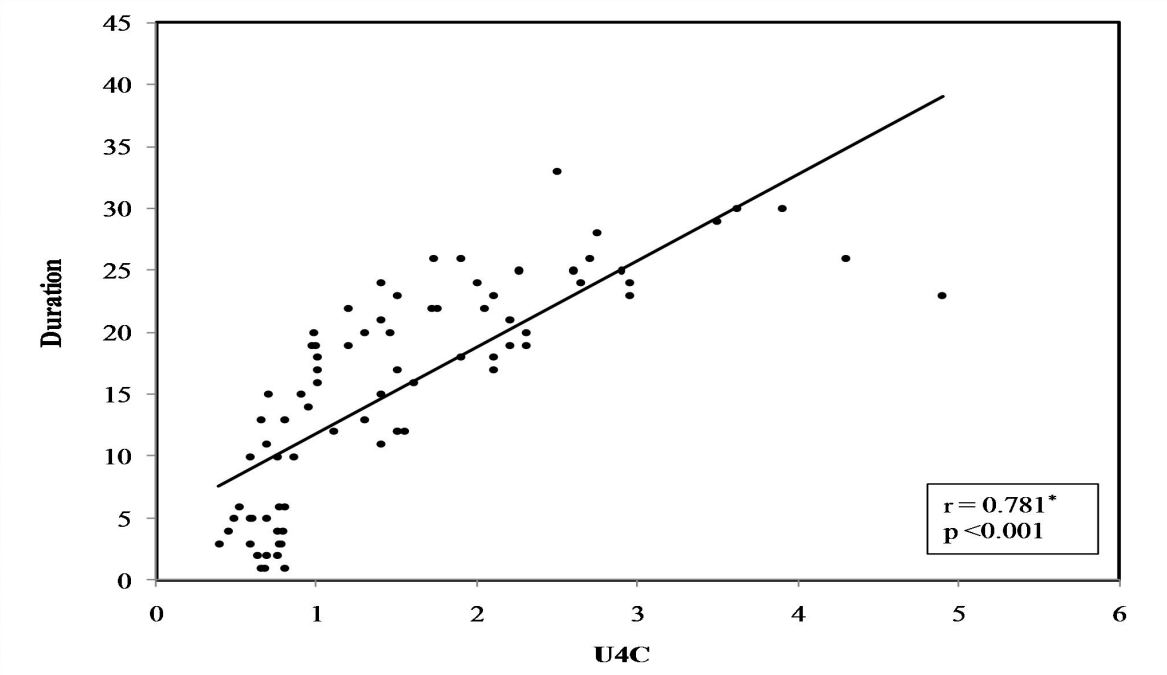


*Figure: (2): Correlation between urinary collagen 4 and diabetes duration.*

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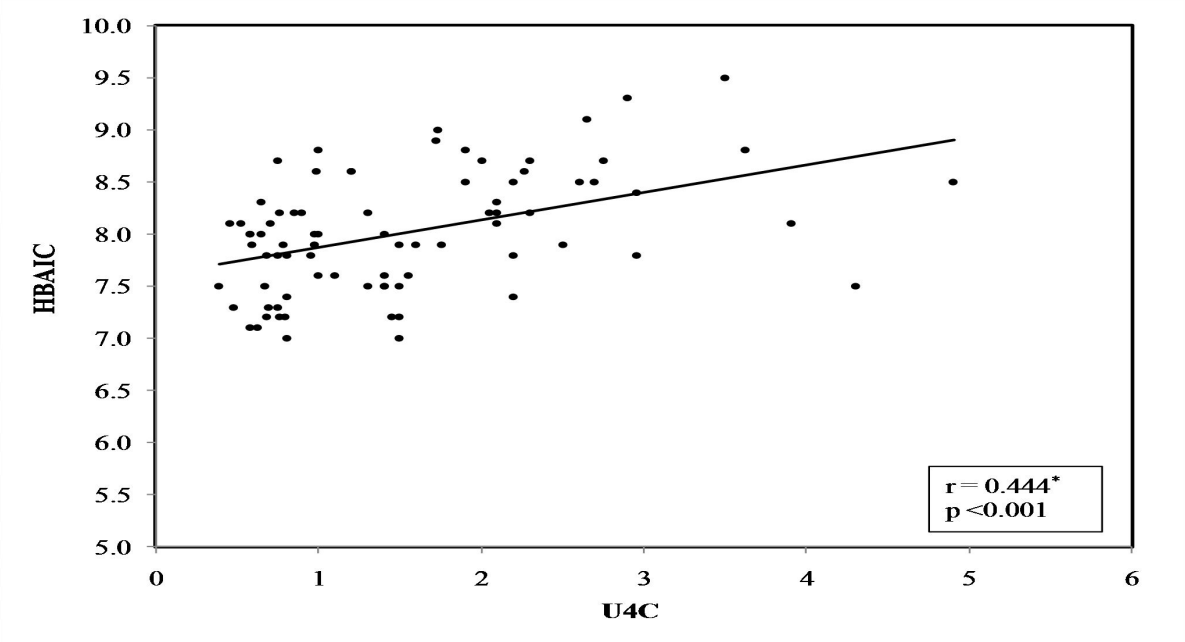


*Figure: (3): Correlation between urinary collagen 4 and HbA1C*

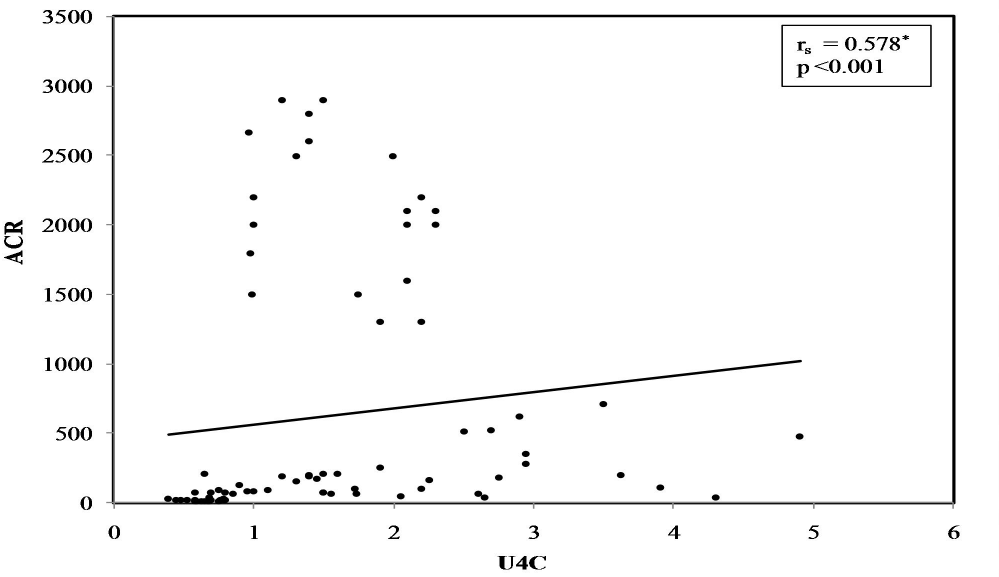


*Figure: (4): Correlation between urinary collagen 4 and ACR.*

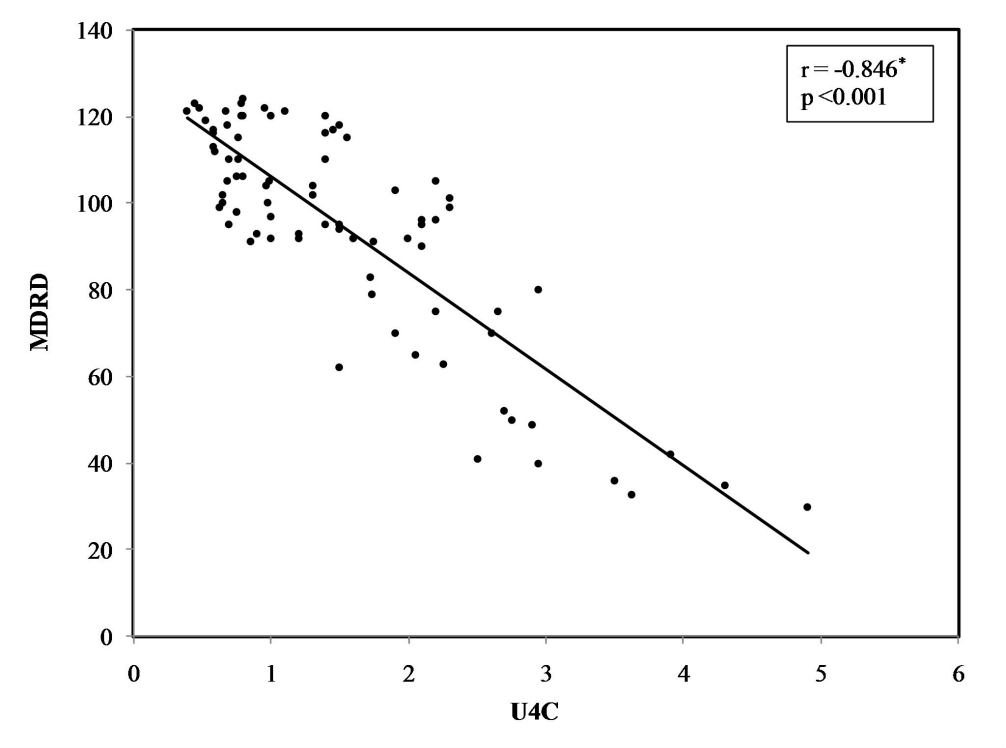


*Figure: (5): Correlation between urinary collagen 4 and MDRD*