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Urinary α-1 microglobulin as a marker of nephropathy in type-2 Diabetes Mellitus

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Abstract:

Background: Type 2 Diabetes Mellitus is the most common cause of Diabetic nephropathy which can progress to end stage renal disease. Early diagnosis can prevent future complications. Hence in-depth studies to detect markers are necessary. Urinary biomarkers can be used as an inexpensive and non-invasive diagnostic tool. α-1-microglobulin is a low molecular weight protein synthesized by the liver. In proximal tubular dysfunction, its concentration in urine is increased. α-1 microglobulin helps in detecting tubular injury so can precede in detecting diabetic nephropathy in its early course.

Aim and Objectives: To determine the role of urinary α-1 microglobulin levels as a marker of nephropathy by comparing it with urinary albumin creatinine ratio and eGFR in type 2 diabetes mellitus

Methods: This cross-sectional study was conducted on random urine samples of subjects with type-2 diabetes mellitus who are on routine follow-up. The subjects were grouped as diagnosed with type 2 diabetes mellitus for more than 5 years and less than 5 years. The urinary α-1 microglobulin-creatinine ratio was correlated to albumin-creatinine ratio, eGFR, and HbA1c levels.

Results: Urinary α-1 microglobulin-creatinine ratio showed a strong positive correlation with albumin-creatinine ratio ($p<0.001$) in subjects with a duration of diabetes less than 5 years and a negative correlation with urinary creatinine ratio ($p<0.001$) in subjects of both groups. Decline in urinary creatinine and eGFR resulted

in an increase in α1-microglobulin-creatinine ratio and is statistically significant in comparison between the 2 groups.

Urinary albumin creatinine ratio was normal in subjects with less than 5year duration of diabetes, however their urinary α-1-microglobulin-creatinine ratio was increased indicating the use of urinary α 1-microglobulin as an early marker.

Conclusion: Urinary α 1-microglobulin can be used as a non-invasive effective tool in the screening of type 2 diabetes mellitus subjects for Diabetic Nephropathy.

Keywords: Urinary α-1 microglobulin; Diabetes Nephropathy; Albumin-Creatinine ratio

Introduction

Diabetic nephropathy is a consequence of long-standing diabetes mellitus. It occurs in 20% to 40% of patients with diabetes.[1] It is associated with an increased risk of mortality, cardiovascular diseases and progression to end-stage renal disease, requiring costly renal replacement therapy in the form of dialysis or transplantation.[2] Early detection is critical in order to delay renal impairment and for better management.

Diabetic nephropathy is usually diagnosed by routine screening tests like urinary albumin and eGFR (estimated-glomerular filtration rate).[1] Although renal biopsy is the gold standard for diagnosis, the majority of patients with diabetes with renal involvement are not biopsied.[3] Currently, microalbuminuria is used as an early marker for the detection of diabetic nephropathy that reflects glomerular damage.[4] In most patients, microalbuminuria occurs after significant renal impairment has occurred.[5] Albuminuria is also associated with exercise, urinary tract infection, acute illness, etc.[2] Due to these limitations, the presence of albumin in the urine cannot be used as an absolute indicator of early diabetic nephropathy.

Urinary biomarkers like α-1microglobulin can be used as an inexpensive and non-invasive diagnostic tool. α-1microglobulin is a low molecular weight glycoprotein, predominantly synthesized in the liver. It is present in various body fluids like serum in its unbound form or bound to Ig A or albumin. [6,7] It is a tissue-cleaning and antioxidant, having reductase, heme, and radical-binding properties.[8]

Due to its low molecular weight and its property of stability in low urinary pH, it can be easily filtered by the glomerular basement membrane which is reabsorbed by proximal tubules. Hence, its content in the urine rises in proximal tubular dysfunction.[9] α-1 microglobulin is mainly synthesized in the liver and distributed throughout the body. It is potent free heme binder. As, the proximal tubule is a major target of ischemic and nephrotoxic injury which induce oxidative stress, α1M urinary excretion was associated with faster chronic kidney disease (CKD) progression and higher mortality. [10, 11]

Increased urinary excretion of α-1 microglobulin can therefore be an early sign of renal damage, primarily on the proximal tubules. Even in patients with type 1 diabetes, increased levels of urinary alpha-1 microglobulin were noted, even when albumin excretion was within normal limits. Additionally, the excretion of Alpha-1 microglobulin from proximal tubules increased with the duration of type 1 diabetes. This study suggested the use of alpha-1 microglobulin as an early marker of proximal tubular impairment in diabetic nephropathy.[12] Studies on urinary α-1 microglobulin and its association with renal impairment in subjects with diabetes in India are sparse and estimation of α-1 microglobulin is not routinely done to examine the extent of renal dysfunction.

Few studies have been able to establish the association between the increased levels of urinary α-1 microglobulin and diabetic nephropathy. However, these studies were conducted on subjects of other ethnicities. As the incidence of diabetic nephropathy differs among populations and is dependent on genetic factors, it is crucial to study nephropathy in Indian diabetic subjects, who are at high risk of developing it.[13] The present study is intended to determine the role of urinary α-1 microglobulin levels as a marker of nephropathy.

Objectives

A. To estimate urinary α-1 microglobulin levels and albumin-creatinine ratio in type-2 diabetes mellitus.
B. To study the relationship between urinary α-1 microglobulin levels, albumin-creatinine

ratio and eGFR in type-2 diabetes mellitus.

Materials and Methods

Study design and Population

The Proposed study was submitted to the Indian Council of Medical Research (ICMR) STS after obtaining clearance from Scientific committee of our institute and it was approved for ICMR STS (Short Term Studentship) 2022 funding (as an undergraduate study)

Ethical consideration

Ethical approval was sought from the Institutional Ethics Committee before the initiation of the study with reference no. MSRMC/EC/SP-02/04-2022. Written informed consent was taken from all the subjects who were chosen to be included in the study. The procedure of sample collection was explained to them along with the implications of the study in a language understood by them.

This cross-sectional study was carried out in the tertiary care teaching hospital at the Clinical Biochemistry diagnostic laboratory in collaboration with the department of Endocrinology

Type of Study

Laboratory investigations

Study population

Type-2 Diabetes Mellitus subjects aged 18 to 65

Inclusion criteria

Subjects aged 18 to 65 who were

A. Newly diagnosed with type-2 diabetes mellitus with HbA1c: 6.5-10%
B. Subjects with a history of type-2 diabetes mellitus with HbA1c: 6.5-10%

Exclusion criteria

Subjects with the following conditions were excluded

a) HbA1c:>10%

b) Type-1 diabetes mellitus

c) Pregnancy and lactation

d) Women on menstruation

e) Hypertension

f) Acute or chronic kidney injury

g) Urinary tract infection

h) On drugs causing proteinuria (NSAIDs, penicillamine, lithium carbonate, antibiotics, opiates, etc.)

Sample size

72 subjects with known case of type-2 diabetes mellitus

Two groups: 36 in each group; divided into subjects with type-2 diabetes mellitus of

duration less than 5 years and more than 5 years.

Sample size justification: Hong, et al. study has observed that the geometric mean of urinary α_1-microglobulin among patients with type 2 diabetes diagnosed below 10 years and above 10 years was 1.19 (95%CI 1.06 -1.33) mg/mmol and 1.43 (95% CI 1.22 – 1.67) mg/mmol respectively. In the present study expecting similar results with 80% power, 95% Confidence level and with an effect

size of 0.66, the study requires a minimum of 36 subjects in each group.

Duration of study

Two months from April 2022 to June, 2022

Informed Consent

The subjects were explained about the procedure and investigations involved and a written informed consent was obtained before the initiation of the study. The subjects also had the option to terminate their involvement as a participant in the study at any given point.

Sample Collection Procedure

After taking a detailed history, the selected type-2 diabetes mellitus subjects who were on routine follow up were grouped based on duration since diagnosis of type-2 diabetes mellitus, as those who had been diagnosed with type-2 diabetes mellitus less than 5 years and who had been diagnosed with type-2 diabetes mellitus more than 5 years.

After explaining the standard collection procedure of the mid-stream urine sample, a random spot urine sample was collected from the subjects who fit the inclusion criteria.

Blood samples were collected as a part of standard routine care for the estimation of serum HbA1c, Postprandial blood sugar (PPBS), Fasting blood sugar (FBS) and serum creatinine.

Sample Processing

Urine samples were centrifuged for 20 minutes, supernatants were isolated and stored at -80°C for later analysis.

- Urinary albumin was estimated by immunoturbidimetry on Ortho Clinical Diagnostics VITROS 5600.
- Urinary creatinine was estimated by modified Jaffe's method.
- Urinary α-1 microglobulin levels were estimated using enzyme-linked immunosorbent assay (ELISA). Urinary α-1 microglobulin-creatinine ratio was calculated to have a standardized value for comparison.
- HbA1c was estimated by HPLC (High Performance Liquid Chromatography) method using Bio-Rad Variant Turbo analyzer.
- PPBS and FBS were measured by hexokinase method.
- Serum creatinine was estimated by modified Jaffe's method.
- eGFR was calculated using serum creatinine values by CKD-EPI Creatinine Equation.

The urinary α-1 microglobulin levels were compared to the albumin-creatinine ratio, eGFR, HbA1c, PPBS and FBS.

Quality control

For serum and urine investigation parameters - external quality control measure - Bio-Rad QC materials were procured and used as per NABL ISO 15189 GUIDELINES and by following Westgard rules of quality control.

Confidentiality

No personal/ identifying details were collected and the study results were anonymized.

Statistical analysis

Data was first tabulated in Microsoft Excel and documented. Descriptive statistics of urinary α-1 microglobulin, albumin-creatinine ratio, eGFR, HbA1c, FBS, and PPBS was analyzed and summarized in terms of mean with standard deviation using Statistical software namely SPSS 22.0, and R environment ver.3.2.2. Microsoft Word and Excel were used to generate graphs.

Independent t test was used to compare the mean α-1 microglobulin, albumin-creatinine ratio, eGFR, HbA1c, FBS, and PPBS between the two groups. Pearson correlation between study variables was performed to find the degree of relationship. The *P*-value was determined by referring to a *t*-distribution with *n*-2 degrees of freedom.

Results

This cross-sectional study was conducted in our institute involving 72 subjects who were grouped based on the duration of type-2 diabetes, into Group 1 of 36 subjects (less than 5 years) and Group 2 of 36 subjects (more than 5 years). All the subjects were being treated for diabetes with oral hypoglycemics or insulin or both. The median time in years since diagnosis was 8.35±8.49.

Descriptive and inferential statistical analysis was carried out for the present study.

Descriptive profile

Out of the total 72 subjects, 33 were males and 39 were females. In group 1, there were 18 males (50%) and 18 females (50%) as depicted in figure 1. In group 2, there were 15 males (41.7%) and 21 females (58.3%) as depicted in figure 2.

The mean age of subjects in years was 53.48±9.37 with a range of 18 to 65 years as depicted in table 1. The frequency of different age groups is depicted in table 1 and figure 3 where the majority belong to the age group >50 years (58.3%).

Comparison of study variables

The blood and urine investigations performed on the two groups are depicted in table 2.

The comparison of study variables in the two groups:

- eGFR in group 1 was higher (88.25±14.8) compared to group 2 (78.86±15.14) which was statistically significant with p value of 0.01.
- Glycemic control given by HbA1c was better in group 2 (7.83±1.33) in comparison with group 1 (8.36±1.53).
- Urinary Creatinine was much more decreased in group 2 (33.35±25.93) compared to group 1 (61.78±38.63) which was statistically significant with p value of <0.001.
- The albumin creatinine ratio was higher in group 2 (2.24±6.38) in comparison with group 1 (0.93±2.28).
- α-1 microglobulin was higher in group 2 (4.63±4.4) than in group 1 (2.42±2.41). The difference was statistically significant with p value of 0.010.

Comparison of clinical variables according to α-1 microglobulin-creatinine ratio

α-1 microglobulin-creatinine ratio was compared with all the study variables in which we observed eGFR and urinary creatinine decreased with an increase in α-1 microglobulin-creatinine ratio and it was statistically significant with p value of 0.027 and <0.001 respectively as shown in Table 3.

Pearson Correlation of Urinary α-1-microglobulin-creatinine ratio with study variables

On correlation of urinary α-1 microglobulin-creatinine ratio with urinary creatinine and albumin-creatinine ratio, we observed that there was a negative correlation with urinary creatinine in both the groups and it was statistically significant with p value of <0.001, whereas with albumin-creatinine ratio it showed a positive correlation in group 1 with p value of <0.001 and values observed in group 2 were not statistically significant as shown table 4.

Discussion

The present study was conducted to evaluate the utility of α-1 microglobulin as a marker in type-2 diabetes mellitus. This is the first study on urinary α-1 microglobulin-

creatinine ratio as a marker of renal dysfunction in patients with type 2 diabetes in India. The present study compared the biochemical parameters in patients with type 2 diabetes with a duration of diabetes of less than and more than 5 years. Diabetic nephropathy presents as lesions in the glomeruli and tubulo-interstitium of the kidney resulting in functional alterations in the kidney that increase albumin excretion in urine and decrease the glomerular filtration rate.[14]

The observations of our study are discussed under the following domains-

1. Urinary α1-microglobulin in type 2 Diabetes mellitus
2. Correlation of Urinary α1-microglobulin with albumin-creatinine ratio
3. Comparison of Urinary α1-microglobulin with HbA1c, PPBS and FBS

1. **Urinary α1-microglobulin in type 2 Diabetes mellitus**

In the present study, urinary α1-microglobulin-creatinine ratio was increased (n=<1.5g/mol) in both the groups, where in group 1 and 2 the mean values were 2.42±2.41 and 4.63±4.4 respectively. Subjects with a longer history of diabetes were found to have greater levels of urinary α-1 microglobulin levels. The results of both groups demonstrate the significance of urinary α-1 microglobulin, which may serve as an early marker in type 2 diabetes and is effective in detecting renal tubular injury. This is in accordance with the study by Hong, et al. [10] α-1 microglobulin is higher in the urine of patients with diabetes when compared to normal subjects. The study also suggests the use of urinary α-1 microglobulin for early detection of tubular dysfunction in diabetic nephropathy.[15]A study conducted on Egyptian patients with type 1 diabetes showed a strong positive correlation between urinary α1-microglobulin and urinary albumin excretion, duration of diabetes, HbA1c, fasting blood glucose, and post prandial blood glucose in children and adolescents. Furthermore, it highlights the significance of tubular dysfunction in these individuals as an early and essential aspect of diabetic nephropathy. [16]A study on proteomic analysis of urinary protein markers for accurate prediction of diabetic kidney disorder demonstrated the presence of additional proteins like alpha-1 microglobulin in urine samples from microalbuminuria-positive patients with type 2 diabetes indicating the need to use these proteins for a better clinical and specific analysis of diabetic nephropathy. [17]

2. Correlation of Urinary α1-microglobulin with albumin- creatinine ratio

A significant positive correlation between urinary α-1 microglobulin and albumin-creatinine ratio was noted in group 1. The mean of albumin-creatinine ratio in g/mol of group 1 and 2 were 0.93±2.28 and 2.24±6.3. The mean urinary α-1 microglobulin-creatinine ratio in g/mol of group 1 and 2 were 2.42±2.41 and 4.63±4.4. In group 1, the albumin-creatinine ratio (n<=1.5) was normal, however α-1 microglobulin-creatinine ratio (n<=1.5) was increased in both the groups, indicating even in normoalbuminuric subjects there was increased urinary excretion of α-1 microglobulin. Similar findings were obtained from a study which reported that patients without microalbuminuria had higher levels of α-1 microglobulin in their urine. Even though urine albumin and α-1 microglobulin are connected, one may exist during the early stages of DN without the other. This suggests that proximal tubular dysfunction may precede glomerular dysfunction and urinary α-1 microglobulin can be used as an early marker for the detection of renal damage. [2, 13, 18]

3. Comparison of urinary α-1 microglobulin with HbA1c, PPBS and FBS

As α-1 microglobulin-creatinine ratio was elevated (n<1.5 g/mol), FBS (140.48±40.78), PPBS (206.09±65.8), and HbA1c (8.11±1.43) were also higher as compared to those values when α-1 microglobulin-creatinine ratio was within the normal range. This suggests that urinary α-1 microglobulin levels were higher in patients with poorer diabetic control, as measured by fasting plasma glucose and postprandial glucose levels, although the difference was not statistically significant. However, there was no correlation found between Hba1c and Urinary α-1 microglobulin levels. A study by Petrica L et al, supports the findings of the present study as no correlations were found between urinary alpha 1-microglobulin and HbA1c. [18]

The cost of urine testing for alpha-1-microglobulin amounts to approximately INR 300 per sample, rendering it comparably affordable when compared to other nephropathy diagnostic tests currently employed. Presently, these tests may not be accessible in semi-urban regions; nonetheless, they can be conveniently utilized within such a setting using minimal resources.

Limitations

The study was conducted on a relatively small sample size of 72 subjects. A larger sample size would provide more conclusive results. Duration of the study was limited to only two months as per ICMR STS (Short Term Studentship) guidelines, which may not have been sufficient to assess the long-term implications of urinary α-1 microglobulin as a marker of nephropathy. Long-term follow-up using samples collected at periodic intervals would provide valuable insights into the predictive value of the urinary α-1 microglobulin. Comparing the urinary α-1 microglobulin with the gold standard like renal biopsy would strengthen the validity of its use as a diagnostic marker.

Conclusion

Our study demonstrates an increase in urinary α-1 microglobulin (marker of tubular dysfunction) in subjects of type-2 diabetes mellitus preceding albuminuria (indicates glomerular dysfunction). Hence urinary α-1 microglobulin is likely to be useful for the early detection of renal disease in type-2 diabetes mellitus. Urinary α-1 microglobulin can also be related to the duration and severity of diabetes. The annual decline of eGFR indicates chronic kidney disease, the most important risk factor of which is proteinuria. The present study shows an increase in urinary α-1microglobulin with a fall in eGFR and urinary creatinine even in normoalbuminuric subjects indicating urinary α1-microglobulin can be used as an early marker of diabetic nephropathy.

Table 1: Age in years -Frequency distribution in two groups of subjects

Age in Years	DM <5 Years	DM >5 Years	Total
<40	6(16.7%)	1(2.8%)	7(9.7%)
40-50	13(36.1%)	10(27.8%)	23(31.9%)
>50	17(47.2%)	25(69.4%)	42(58.3%)
Mean ± SD	50.41±9.39	56.55±8.41	53.48±9.37

Table 2: Comparison of study variables - in two groups of patients studied.

Variables	Group 1 (DM<5YRS)	Group 2 DM >5 YRS	Total	P Value
eGFR(ml/min/1.73m^2)	88.25±14.8	78.86±15.14	83.56±15.6	0.010*
HbA1c (%)	8.36±1.53	7.83±1.33	8.09±1.45	0.121

Serum Creatinine (mg/dl)	0.93±0.15	0.97±0.17	0.95±0.16	0.314
FBS (mg/dl)	141.69±44.95	132.53±34.03	137.11±39.85	0.333
PPBS (mg/dl)	215.14±70.43	194.92±57.96	205.03±64.84	0.188
Urinary Creatinine(µmol/l)	61.78±38.63	33.35±25.93	47.57±35.67	<0.001**
Albumin-creatinine ratio(mg/mmol)	0.93±2.28	2.24±6.38	1.59±4.8	0.249
α-1 microglobulin - creatinine ratio(g/mol)	2.42±2.41	4.63±4.4	3.53±3.69	0.010*

* Moderately significant (P value: 0.01<P< 0.05)

** Strongly significant (P value: P<0.01)

Table 3: Comparison of clinical variables according to α-1 microglobulin-creatinine ratio

Variables	α-1 microglobulin-creatinine ratio		Total	P Value
	<1.5 g/mol	>1.5 g/mol		
Duration of DM (years)	5.58±6.66	9.91±9.07	8.35±8.49	0.037*
Height (cm)	165.13±6.94	162.55±4.55	163.49±5.63	0.061+
Weight (kg)	67.27±12.96	70.39±14.27	69.26±13.8	0.360
BMI (kg/m^2)	24.85±5.13	26.61±4.98	25.97±5.07	0.158
eGFR (ml/min/1.73 m^2)	88.92±12.87	80.52±16.31	83.56±15.6	0.027*
HbA1C (%)	8.05±1.51	8.11±1.43	8.09±1.45	0.861
Serum Creatinine (mg/mmol)	0.95±0.16	0.95±0.16	0.95±0.16	0.967
FBS (mg/dl)	131.15±38.19	140.48±40.78	137.11±39.85	0.344
PPBS (mg/dl)	203.15±64.36	206.09±65.8	205.03±64.84	0.855
Albumin-creatinine ratio (mg/mmol)	1.5±6.58	1.63±3.51	1.59±4.8	0.908
Urinary creatinine (mg/mmol)	83.4±32.71	27.31±15.84	47.57±35.67	<0.001**

+ Suggestive significance (P value: 0.05<P<0.10)

* Moderately significant (P value: 0.01<P< 0.05)

** Strongly significant (P value: P<0.01)

Table 4: Pearson Correlation

Correlation of α-1-microglobulin-creatinine ratio	DM<=5YRS		DM >5 YRS	
	r value	p value	r value	p value
Urinary Creatinine	-0.683	<0.001**	-0.599	<0.001**
Albumin-creatinine ratio	0.586	<0.001**	-0.098	0.568

** Strongly significant (P value: P<0.01)

References

1. Bae J, Won YJ, Lee BW. Non-albumin proteinuria (NAP) as a complementary marker for diabetic kidney disease (DKD). Life. 2021;11(3):1-12.
2. Fiseha T. Urinary biomarkers for early diabetic nephropathy in type 2 diabetic patients. Biomark Research. 2015;3(1):1-7.
3. Qi C, Mao X, Zhang Z, Wu H. Classification and Differential Diagnosis of Diabetic Nephropathy. Journal of Diabetes Research. 2017; 2017:1-17.
4. Robles-Osorio ML, Sabath E. Tubular dysfunction and non-albuminuric renal disease in subjects with type 2 diabetes mellitus. Revista de Investigacion Clinica. 2014;66(3):234-239.
5. Rigalleau V, Lasseur C, Raffaitin C, Beauvieux MC, Barthe N, Chauveau P et al.Normoalbuminuric Renal-Insufficient Diabetic Patients. Diabetes Care. 2007; 30:2034–9.
6. Itoh Y, Kawai T. Human alpha-1 microglobulin levels: Its measurement and clinical significance. Journal of Clinical Laboratory Analysis. 1990; 4:376–80.
7. Andersson L, Haraldsson B, Johansson C, Barregard L. Methodological issues on the use of urinary alpha-1-microglobulin in epidemiological studies. Nephrology Dialysis Transplantation.2008;23(4):1252-6.
8. Bergwik J, Kristiansson A, Allhorn M, Gram M, Åkerström B. Structure, Functions, and Physiological Roles of the Lipocalin α1-Microglobulin (A1M). Frontiers in Physiology.2021;12:251.
9. Ekstrom B, Peterson PA, Berggard I: A urinary and plasma α1-glycoprotein of low molecular weight: isolation and some properties. Biochem Biophys Res Commun. 1975; 65:1427–33.
10. Zager RA. Alpha 1 Microglobulin: A Potentially Paradoxical Anti-Oxidant Agent. Adv Tech Biol Med. 2017; 5:238.
11. Robles NR, Lopez Gomez J, Garcia Pino G, Valladares J, Hernandez Gallego R et al; Alpha-1-microglobulin: Prognostic value in chronic kidney disease. Med Clin (Barc). 2021;157(8):368-70.
12. Pfleiderer S, Zimmerhackl LB, Kinne R, Manz F, Schuler G, Brandis M. Renal proximal and distal tubular function is attenuated in diabetes mellitus type 1 as determined by the excretion of alpha-1 microglobulin and Tamm-Horsfall protein.Clin Investig. 1993; 71:972–7.
13. Hong CY, Hughes K, Chia KS, Ng V, Ling SL. Urinary α1-microglobulin as a marker of nephropathy in type 2 diabetic Asian subjects in Singapore. Diabetes Care. 2003;26(2):338-342.
14. A Kalansooriya, I Holbrook, P. Jennings & P H Whiting. Serum cystatin C, enzymuria, tubular proteinuria and early renal insult in type 2 diabetes, British Journal of Biomedical Science. 2007;64(3):121-23
15. Shore N, Khurshid R, Saleem M. Alpha-1 microglobulin: a marker for early detection of tubular disorders in diabetic nephropathy. J Ayub Med Coll Abbottabad. 2010;22(4):53-55
16. Saif A, Soliman N. Urinary α1-microglobulin and albumin excretion in children and adolescents with type 1 diabetes. J Diabetes. 2017;9(1):61-64.
17. Jain S, Rajput A, Kumar Y, Uppuluri N, Arvind AS, Tatu U. Proteomic analysis of urinary protein markers for accurate prediction of diabetic kidney disorder. J Assoc Physicians India. 2005; 53:513-20.
18. Petrica L, Petrica M, Vlad A, Jianu DC, Gluhovschi G, Ianculescu C, et al. Proximal tubule dysfunction is

dissociated from endothelial dysfunction in normoalbuminuric patients with type 2 diabetes mellitus: a cross-sectional study. Nephron Clin Pract. 2011;118(2):c155-64.

Legends Figures

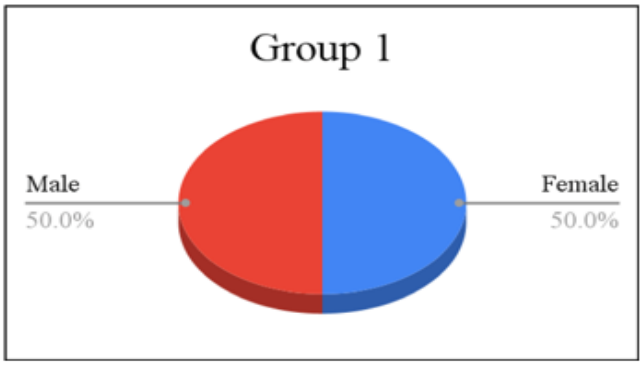

Figure 1: Gender-Frequency distribution in Group 1

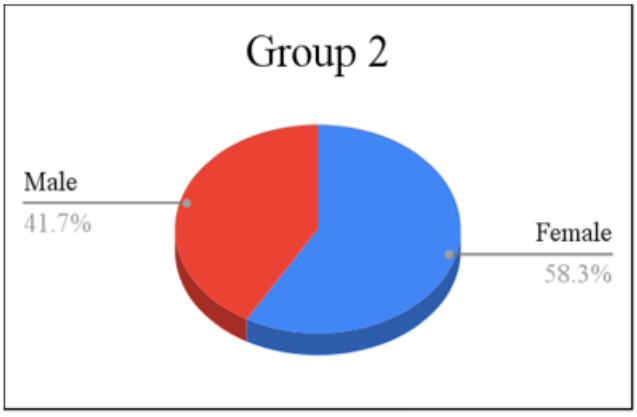

Figure 2: Gender-Frequency distribution in Group 2

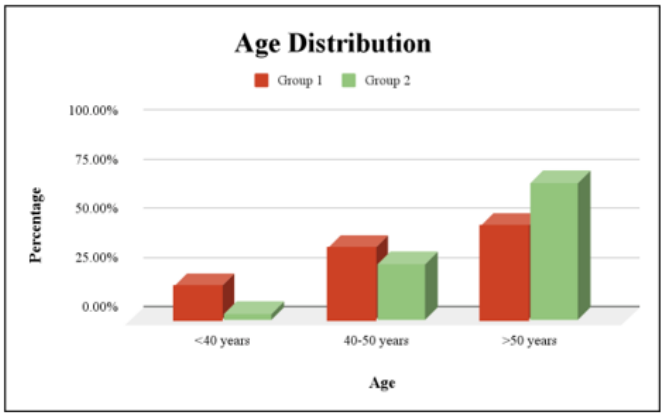

Figure 3: Age in years -Frequency distribution in two groups of subjects