Proceedings S.Z.P.G.M.I. Vol: 32(1): pp. 13-16, 2018. PSZMC-663-32-1-2018

# Evaluation of Urinary Gamma Glutamyl Transferase as an Early Biomarker of Diabetic Nephropathy in Type 2 Diabetic Patients

**Shazia Hameed, Mahnoor Khan, Tahira Naseem**

*Department of Biochemistry and Chemical Pathology, Shaikh Zayed Medical Complex, Lahore*

## ABSTRACT

**Introduction:** Diabetic nephropathy is one of the most common diabetic complication that is diagnosed by current markers of renal function namely serum creatinine and creatinine clearance. Elevated serum creatinine and a decline in creatinine clearance is the indication of nephropathy. Mostly, this disease is detected at a much later stage due to the lack of sensitivity and specificity of these renal function markers. Keeping in view the need of a more sensitive and specific biomarker of diabetic nephropathy, this research aimed to evaluate urinary enzyme, Gamma Glutamyl Transferase (uGGT) as a biomarker of renal injury in type – 2 diabetic patients. **Aims and Objectives:** To compare uGGT with serum creatinine and creatinine clearance as biomarkers of renal injury in type 2 diabetic patients. **Place and Duration of Study:** This study was conducted at Shaikh Zayed Hospital, Lahore in the department of Biochemistry & Chemical Pathology and was completed in 3 months. **Material and Methods:** Study included 100 subjects, out of which 75 (41 males and 34 females) were type-2 diabetics and 25 (15 males and 10 females) were healthy controls. uGGT and serum creatinine were measured on Dimension AR clinical chemistry Auto Analyzer. Creatinine clearance was calculated by using the Cockcroft and Gault formula. **Results:** uGGT levels were compared with serum creatinine and creatinine clearance of the Diabetic and the Control group. The diabetic group showed increased levels of uGGT as compared to controls, whereas their serum creatinine and creatinine clearance were not significantly different from controls. **Conclusion:** These findings indicate the increase of uGGT precedes the rise in serum creatinine and decrease in creatinine clearance. Thus, raised uGGT maybe suggestive of the initial phase of diabetic nephropathy.

**Key words:** uGGT, Diabetic Nephropathy, Creatinine and Creatinine Clearance.

## INTRODUCTION

Diabetic nephropathy is one of the most common micro vascular complications of Diabetes Mellitus which greatly affects the life quality and survival of the patients[1]. It develops in more than 40% of all type-2 diabetic patients. For quite a long time, the impaired renal function of these patients is assessed by serum creatinine and blood urea nitrogen, both of which are insensitive to early changes in renal function.[2]

Serum creatinine has been used to screen for kidney diseases for more than a century.[3] Moreover, it is influenced by mass, gender, age, race, medications and is not elevated till the injury becomes well established.[4] Serum creatinine level rises in blood in parallel to the degree of renal injury but further research has revealed that a substantial number of patients have evidence of tubular injury without a significant elevation in their serum creatinine, which is actually a reflection of glomerular injury that occurs late.[5] Creatinine clearance correlates better with GFR than creatinine but it can only signify whether renal function is normal, moderately or severely reduced.[6] Compromised renal function leads to less clearance of creatinine from the blood thus lowering its levels. Therefore, serum creatinine levels are directly proportional and creatinine clearance is inversely proportional to the renal function. Wu and Parikh

have observed that serum creatinine and creatinine clearance are late biomarkers of diabetic nephropathy.[4] This conclusion stresses the need to search for a more sensitive and more specific marker of renal function that can detect diabetic nephropathy in its earliest stage. This research aims to evaluate Urinary Gamma Glutamyl Transferase (uGGT) as a more sensitive biomarker of renal injury than serum creatinine and creatinine clearance in type 2 diabetic patients.

GGT is an enzyme primarily located in the brush border of the proximal convoluted tubules of the kidney. Early renal damage is characterized by increased proximal tubular enzymeuria and uGGT is one of the enzymes that get markedly elevated in the initial phase of renal tubular injury.[8] Another study found it to be even more specific for nephropathy than other urinary enzymes e.g. Dipeptidyl amino peptidase IV and Alanine Aminopeptidase.[10] It was also found to be directly proportional to proteinuria which is a major but late manifestation of nephropathy.[9] Owing to its unique localization and due to the early and marked response to nephropathy, uGGT has gained importance as an emerging, sensitive biomarker of renal injury. This study aims to compare this new renal injury marker with the currently used renal function markers to assess its utility as a biomarker of diabetic nephropathy which may one day replace the existing less sensitive and less specific renal biomarkers.

## MATERIAL AND METHODS

In this study, one hundred study subjects both males and females were divided into two groups i.e. Diabetic Group and Control Group. The Diabetic group consisted of 75 patients (41 males and 34 females) and the Control Group had 25 healthy subjects (15 males and 10 females). The criteria for inclusion in the Diabetic Group was diagnosed type 2 Diabetes Mellitus for 10-18 years with normal serum creatinine. Patients having increased serum creatinine, history of any acute or chronic renal disease, renal transplant, present pregnancy or any other diagnosed systemic disease or malignancy were excluded.

Serum creatinine estimation was performed on the Dimension AR Clinical Chemistry Auto Analyzer. The Kit was purchased by Siemens Health Care, Diagnostics. Creatinine Clearance was calculated by CG formula (Cockcroft and Gault), proposed in 1976.[11]

uGGT was performed on Dimension AR Clinical Chemistry Auto Analyzer. The reported normal range of uGGT is 16.17±2.92 units / gram of creatinine.[12]

**Statistical Analysis:**

Statistical analysis was done on SPSS version 15.0. Results of uGGT, serum creatinine and creatinine clearance were expressed as mean ± SEM. Students't' test was used for comparison between two groups. A ''pvalue'' of less than 0.05 was considered statistically significant.

## RESULTS

There was no significant difference between the mean age, weight, height and BMI of the Diabetic and Control groups (Table-1). The mean serum creatinine and creatinine clearance of male and female diabetics was not found significantly different from that of the controls (Table-2).

The mean uGGT of male diabetics was significantly higher ($p<0.001$) as compared to that of the male controls. Similarly, mean uGGT of female diabetics was also found to be significantly higher ($P <0.001$) than female controls (Table -2).

## DISCUSSION

It is documented that, the initial phase of Diabetic nephropathy is marked by proximal tubular enzymeuria followed by glomerular injury.[8] GGT is one of the enzyme present in the proximal tubular cells of the kidney which appears in the urine as soon as renal injury is initiated. Therefore, this study was designed to detect whether uGGT levels precede the rise in serum creatinine and decrease in creatinine clearance or not.

As serum creatinine and creatinine clearance of all the diabetics was not significantly different as compared to the controls, therefore these markers did not reflect presence of diabetic nephropathy in these patients.

| Group | Male | | Female | |
|---|---|---|---|---|
| | Control (n=15) | Diabetics (n=33) | Controls (n=10) | Diabetics (n=42) |
| **Age (yr)** | 50.80 ± 1.70 | 52.10 ± 1.09 | 50.80 ± 3.00 | 50.44 ± 1.88 |
| **Weight (Kg)** | 71.73 ± 1.08 | 72.54 ± 0.91 | 70.80 ± 2.12 | 72.85 ± 1.22 |
| **Height (m)** | 1.64 ± 0.01 | 1.62 ± 0.01 | 1.62 ± 0.02 | 1.62 ± 0.01 |
| **BMI (kg/m$^2$)** | 24.47 ± 0.79 | 28.32 ± 0.36 | 26.50 ± 1.18 | 28.68 ± 0.45 |
| **Systolic BP (mm Hg)** | 117.33 ± 1.82 | 121.95 ± 1.89 | 118.00 ± 1.33 | 123.24 ±1.62 |
| **Diastolic BP (mm Hg)** | 80.33 ± 1.72 | 82.68 ± 1.48 | 82.60 ± 1.37 | 83.82 ± 1.69 |
| **FBG (mg/dl)** | 81.27 ± 2.05 | 239.80 ± 6.63** | 82.40 ± 2.84 | 226.94 ± 6.94** |

** p< 0.001 significantly higher as compared to control.

**Table-1:** Age, weight, height, BMI, systolic BP, diastolic BP, FBG, in male and female groups. Mean ± SEM is given. Figure in parenthesis indicates number of cases in each group.

| Group | Male | | Female | |
|---|---|---|---|---|
| | Control (n=15) | Diabetics (n=33) | Controls (n=10) | Diabetics (n=42) |
| **Urinary uGGT (U/L)** | 3.60 ± 0.84 | 31.05 ± 4.63** | 3.30 ± 0.94 | 36.44 ± 6.39** |
| **Serum Creatinine (mg/dl)** | 1.05 ± 0.09 | 1.13 ± 0.23 | 0.81 ± 0.05 | 1.24 ± 0.064 |
| **Creatinine Clearance (ml/min)** | 107.13 ± 21.31 | 87.76 ± 20.83 | 100.20± 4.21 | 82.12 ± 4.66 |

** p< 0.001 significantly higher as compared to control.

**Table-2:** Urinary GGT, serum creatinine and creatinine clearance in male and female groups. Mean ± SEM is given. Figure in parenthesis indicates number of cases in each group.

A similar study in this regard reported, that many patients show evidence of tubular injury without a significant rise in their serum creatinine.[5] Creatinine clearance was also not found significantly different as compared to the controls. These results are in agreement to those reported by Wu and Parikh who observed that both serum creatinine and creatinine clearance are known to be late biomarkers of diabetic nephropathy.[4] On the other hand all type-2 diabetic patients had elevated uGGT levels when compared to a well matched control group. These results of the diabetic group are in accordance with the results reported in the studies performed by Ambade and Dedov.[8] In these studies type 2 diabetic patients with similar duration of diabetes had significantly higher values of uGGT in comparison to the controls.

As uGGT is a tubular enzyme, these raised levels may be the manifestation of renal tubular injury in these diabetic patients. Moreover, it was observed that raised uGGT was found without concurrent rise in serum creatinine or the fall in creatinine clearance.[13] These significantly raised levels of uGGT may be the manifestation of the renal tubular injury in these patients. This study may suggest that uGGT may be more sensitive in detecting the initial phase of diabetic nephropathy which may not be detected by the conventional renal function markers used these days. Further research in this regard with a larger sample size shall be more appropriate to assess the diagnostic role of uGGT in renal injury.

## CONCLUSION

It can be concluded from the present study, that Type – 2 Diabetics having 10 – 18 years of duration of the disease had increased levels of urinary GGT with normal serum creatinine and creatinine clearance. Hence, it may be concluded from this study that excretion of uGGT may precede the rise in serum creatinine and fall in creatinine clearance in diabetics who are prone to develop diabetic nephropathy. Therefore, early detection of nephropathy can help in the timely management of these patients.

## REFERENCES

1. Rossing K, Christensen PK, Horind P, Tarnon L, Rossing P, Parving HH. Progression of nephropathy in type-2 diabetic. Kidney International 2004; 66: 1596 – 605.

2. Yang YH, He XJ, Chen SR, Wang L, Li EM, Xu LY. Changes of serum and urine NGAL in type 2 diabetic patients with nephropathy one year observational follow up study. Endocrine 2009; 36: 45 – 51.
3. Rehberg PB. Studies on kidney function: the rate of filtration and re-absorption in human kidney. Biochemist J 1926; 20: 447 – 60.
4. Wu I, Parikh CR. Screening for kidney disease: older measures versus novel biomarkers. Clin J Am SocNephrol 2008; 3: 1895 – 901.
5. Gwinner W, Hinzmann K, Erdbrneggar U, Scheffner I, Broecker V, Vaske B et al. Acute tubular injury in protocol biopsies of renal grafts. Prevalence, associated factors and effect on long term function. Am J Transplant 2008; 8: 1684 – 93.
6. Sarah W, Gojka R, Anders G, Richard S, Hilary K. Global Prevalance of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes care 2004;27(5): 1047 – 53.
7. Piscator M. Early detection of tubular dysfunction kidney Internation 1991; 40 (Suppl 34): 15 – 7.
8. Ambade V, Singh P, Somani BL, Basannar D. Urinary N-Aceyl Beta Glucosaminidase and Gamma Glutamyl Transferase as early markers of Diabetic Nephropathy. Indian Journal of Clinical Biochemistry 2006; 21(2): 142 – 8.
9. Wilfred K, Josph N, Makumi. Eluid M, Christine S, Seth O. Evaluation of urinary tubular enzymes as screening markers of renal dysfunction in patients suffering from Diabetes Mellitus. Asian Journal of Medical Sciences 2011; 5(3): 84 – 90.
10. Ikenaga H, Suzuki H, Ishii N, Itoh H, Saruta T. Enzymeuria in non-insulin dependant diabetic patients: sings of tubular cell dysfunation. Clin Sci 1993; 84 (4): 469 – 75.
11. Lamb E, Newmann DJ, Price CP. Kidney function Test. In; Tietz Text Book of Clinical Chemistry and Molecular Diagnostics. Burtis CA, Ashwood ER, Burns DE. 4$^{th}$ed, India: Elsevier; 2006; p – 822.
12. Zhang H, Forman HJ, Redox regulation of ɣ - glutamyl Transpeptidase. Am J Biol 2009; 41(5): 509 – 15.
13. Phillips AO. The role of renal proximal tubular cells in diabetic nephropathy. Curr Diab Rep 2003; 3(6): 491 – 6.

**The Authors:**

Shazia Hameed,
Department of Biochemistry and Chemical Pathology, Shaikh Zayed Medical Complex, Lahore

Mahnoor Khan,
Department of Biochemistry and Chemical Pathology, Shaikh Zayed Medical Complex, Lahore

Tahira Naseem
Department of Biochemistry and Chemical Pathology, Shaikh Zayed Medical Complex, Lahore

**Corresponding Author:**

Dr. Shazia Hameed
Department of Biochemistry and Chemical Pathology, Shaikh Zayed Medical Complex, Lahore
Contact No. 03004149395
e-mail: drshazia137@gmail.com