Gamma-Glutamyl Transferase is Related to Microalbuminuria in Diabetic Patients

Gamma-Glutamil Transferaz Diyabetik Hastalarda Mikroalbüminüri ile İlişkilidir

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ABSTRACT

OBJECTIVE: In this study, we aimed to investigate whether serum GGT levels are associated with microalbuminuria in patients with diabetes mellitus.

MATERIAL and METHODS: The study included 107 diabetic patients. Albuminuria was assessed using urinary albumin creatinine ratio (UACR). Normoalbuminuria and microalbuminuria were defined as UACR <0.030 and UACR of 0.030-0.300, respectively.

RESULTS: Fifty-six (52.3%) of the 107 patients had microalbuminuria, whereas 51 (47.7%) patients were normoalbuminuric. Serum GGT levels were significantly higher in patients with microalbuminuria than in those with normoalbuminuria [27 (4-315) IU/L vs. 21 (8-77) IU/L, p: 0.011; respectively]. Serum GGT values were divided as high or low according to the median value. High serum GGT levels were more frequent in patients with microalbuminuria than in those with normoalbuminuria [35 (62.5%) vs. 17 (33.3%), p: 0.002]. UACR value s were positively correlated with the serum GGT level (r: 0.331, p: <0.001), age (r: 0.195, p: 0.044), and duration of diabetes mellitus (r: 0.202, p: 0.037), and negatively correlated with estimated glomerular filtration rate (eGFR) (r: -0.441, p: <0.001). In the multivariate analysis (binary logistic regression analysis), eGFR and GGT status were found to be independent risk factors for microalbuminuria.

CONCLUSION: Serum GGT levels were significantly higher in microalbuminuric diabetic patients. The underlying cause of this finding should be elucidated.

KEY WORDS: Diabetes mellitus, Gamma-glutamyltransferase, Microalbuminuria

ÖZ

AMAÇ: Bu çalışmada, diyabetik hastalarda serum GGT düzeyleri ile mikroalbüminüri arasında bir ilişkinin olup olmadığını araştırmayı amaçladık.

GEREÇ ve YÖNTEMLER: Çalışmaya 107 diyabetik hasta dahil edildi. Albüminüri idrar albümin kreatinin oranı (İAKO) kullanılarak değerlendirildi. Normoalbüminüri ve mikroalbüminüri sırasıyla İAKO'nın 0,030'dan düşük olması ve İAKO'nın 0,030-0,300 arasında olması şeklinde tanımlandı.

BULGULAR: Elli altı (%52,3) hasta mikroalbüminüriye sahip iken, 51 (%47,7) hasta normoalbüminürikti. Serum GGT düzeyleri mikroalbüminürik hastalarda normoalbüminürik olanlara kıyasla anlamlı olarak daha yüksekti [sırasıyla 27 (4-315) IU/L'ye karşın 21 (8-77) IU/L, p: 0,011]. Hastalar serum GGT düzeylerinin ortanca değerine göre yüksek veya düşük olarak ikiye ayrıldı. Yüksek serum GGT grup, normoalbüminürik olanlara kıyasla, mikroalbüminürik hastalarda anlamlı olarak daha sıktı [sırasıyla 35 (%62,5)'e karşın 17 (%33,3), p: 0,002]. İdrar albümin kreatinin oranı, serum GGT düzeyi (r: 0,331, p: <0,001), yaş (r: 0,195, p: 0,044), ve diyabet süresi (r: 0,202, p: 0,037) ile doğru orantılı, hesaplanmış glomerüler filtrasyon hızı (eGFR) (r: -0,441, p: <0,001) ile ters yönde koreleydi. Çoklu değişken analizinde (ikili lojistik regresyon analizi) eGFR ve GGT grubu mikroalbüminüri için bağımsız risk faktörleri olarak saptandı.

SONUÇ: Serum GGT düzeyleri mikroalbüminürik diyabetik hastalarda anlamlı olarak yüksektir. Bu bulgunun altta yatan nedenlerinin aydınlatılmaya ihtiyacı vardır.

ANAHTAR SÖZCÜKLER: Diabetes mellitus, Gamma-glutamil transferaz, Mikroalbüminüri

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INTRODUCTION

Diabetic nephropathy is a leading cause of morbidity and mortality in diabetic patients representing a huge health and economic burden (1). Diabetic nephropathy (DN) is typically defined by macroalbuminuria (i.e. a urinary albumin excretion of more than 300 mg/day) or macroalbuminuria and abnormal renal function as represented by an abnormality in serum creatinine or glomerular filtration rate (GFR) (2). Persistent albumin excretion between 30 and 300 mg/day is called microalbuminuria and, in patients with diabetes mellitus (particularly type 1 diabetes mellitus), may be indicative of early diabetic nephropathy, unless there is some coexistent renal disease (3).

Microalbuminuria is associated with an increased risk of cardiovascular disease (CVD) in patients with diabetes mellitus (4). The mechanisms of the relationship between microalbuminuria and CVD risk are not well understood but may be related to increased transvascular leakiness of albumin in systemic as well as renal vessels (5). Microalbuminuria is a marker of endothelial dysfunction or generalized vasculopathy that may lead to atherogenic states (5), and endothelial dysfunction possibly precedes development of microalbuminuria in patients with diabetes mellitus (6). Persistent microalbuminuria also seems to be associated to poor blood pressure control (7).

Gamma-glutamyltransferase (GGT) is an enzyme located on the plasma membranes of several cells and tissues with a predominance of the liver (8). It has been reported that GGT might be an early and sensitive marker of oxidative stress even when within the normal range (9) and is related to a greater risk of hypertension, incident diabetes mellitus, CVD, CVD-associated mortality, and all-cause mortality as well as endothelial function in chronic kidney disease (10-13).

In this study, we aimed to investigate whether serum GGT levels were associated with microalbuminuria in patients with diabetes mellitus.

MATERIAL and METHODS

This study included 107 patients with diabetes mellitus. We recorded the biochemical measurements at their last follow-up examination. We also noted demographic data such as gender. None of these patients had a history of alcohol drinking and liver disease.

The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula (14). Albuminuria was assessed using the urinary albumin creatinine ratio (UACR). Urine albumin and creatinine concentrations were measured three times in the microalbuminuric group except 9 patients in whom these measurements were performed two times. On the other hand, all these measurements were performed only once in the normoalbuminuric group. Normoalbuminuria and microalbuminuria were defined as UACR <0.030 and UACR of 0.030-0.300, respectively.

Dyslipidemia was defined as follows: serum low-density lipoprotein (LDL) cholesterol ≥160 mg/dL or total cholesterol ≥240 mg/dL or triglyceride ≥200 mg/dl or high-density lipoprotein (HDL) cholesterol <40 mg/dl or use of an antihyperlipidemic agent (15).

The statistical analysis was performed using the SPSS 15.0 software (SPSSFW; SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine normality of distributions of variables. Continuous variables with normal distribution are presented as mean ± SD. The median value was used where a normal distribution was absent. Statistical analysis for the parametric variables was performed using Student's t-test between two groups. The Mann-Whitney U test was used to compare nonparametric variables between two groups. The correlation analysis was evaluated by Pearson's correlation test. Qualitative variables were given as percents and the correlation between categorical variables was investigated using the chi-square test and Fisher's exact test. Binary logistic regression analysis (multivariate analysis) was performed to determine the relationship between microalbuminuria and the following variables: age, gender, duration of diabetes mellitus, presence of hypertension, use of angiotensin converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB), GGT group, presence of dyslipidemia, and eGFR. A *P* value of <0.05 was considered significant.

RESULTS

Table I shows characteristics of the 107 patients with diabetes mellitus. The mean age was 59 ± 11 years and the majority of the patients were female. The median serum GGT level was 24 IU/L. The median UACR was 0.040 (range 0.001 to 0.300) whereas the mean eGFR was 82.6 ± 28.6 mL/min. Only 7 patients had type 1 diabetes mellitus whereas 100 patients had type 2 diabetes mellitus. Median duration of diabetes mellitus was 7.0 years. The majority of the patients had hypertension whereas approximately half of the patients received ACEI or ARB. Fifty-six (52.3%) of 107 patients had microalbuminuria whereas 51 (47.7%) patients were normoalbuminuric. Table II shows the comparison of the demographic, clinical, and biochemical parameters between the patient groups. Levels of serum GGT, total cholesterol, and LDL cholesterol, UACR value, presence of hypertension, and use of ACEI or ARB were significantly higher in patients with microalbuminuria compared to those with normoalbuminuria. Serum GGT values were divided as high or low according to the median value. A high serum GGT was more frequent in patients with microalbuminuria than in those with normoalbuminuria. The eGFR value was significantly lower in patients with microalbuminuria than in those with normoalbuminuria. On the other hand, there was no significant difference between the two groups in terms of age, gender, type and duration of diabetes mellitus, systolic and diastolic blood pressure measurements, smoking, presence of coronary artery disease and dyslipidemia, use of statin, HbA1c value, and

Table I: Patient characteristics.

Age (year)	59 ± 11
Female/male	66 (61.7%)/41 (38.3%)
Type of diabetes mellitus	
Type 1 (%)	7 (6.5)
Type 2 (%)	100 (93.5)
Duration of diabetes mellitus (year)	7.0 (1.0-32.0)
Anti-glycemic treatment	
Metformin (%)	52 (48.6)
Sulfonylurea (%)	16 (15.0)
Insulin (%)	63 (58.6)
Vildagliptin (%)	2 (1.9)
Presence of hypertension (%)	65 (60.7)
Presence of coronary artery disease (%)	25 (23.4)
Use of statin (%)	21 (19.6)
Use of ACEI or ARB (%)	53 (49.5)
Presence of congestive heart failure (%)	3 (2.8)
Presence of cerebrovascular disease (%)	2 (1.9)
Smoking	
Never (%)	96 (89.7)
Active smoker (%)	7 (6.5)
Ex-smoker (%)	4 (3.7)
Systolic blood pressure (mmHg)	130 (100-210)
Diastolic blood pressure (mmHg)	80 (60-120)
Serum GGT level (IU/L)	24 (4-315)
Urinary albumin creatinine ratio	0.040 (0.001-0.300)
HbA1c (%)	6.4 (4.5-12.5)
Serum glucose (mg/dL)	128 (67-467)
Triglyceride (mg/dL)	147 (58-1105)
Total cholesterol (mg/dL)	190 ± 39
Low-density lipoprotein cholesterol, (mg/dL)	114 ± 35
High-density lipoprotein cholesterol (mg/dL)	43 ± 9
Serum albumin (g/dL)	4.1 ± 0.3
eGFR (ml/min)	82.6 ± 28.6

ACEI: Angiotensin converting enzyme inhibitor, **ARB:** Angiotensin II receptor blocker, **GGT:** Gamma glutamyl transferase, **eGFR:** Estimated glomerular filtration rate

levels of serum glucose, triglyceride, HDL cholesterol, alanine aminotransferase, alkaline phosphatase, and albumin.

The UACR value positively correlated with serum GGT level (r: 0.331, *p:* <0.001), age (r: 0.195, *p:* 0.044), duration of diabetes mellitus (r: 0.202, *p*: 0.037), and systolic blood pressure (r: 0.208, *p*: 0.031) and negatively correlated with eGFR (r: -0.441, *p:* <0.001), but it did not correlate with HbA1c, serum glucose level, and diastolic blood pressure. Serum GGT level positively correlated with age (r: 0.212, *p:* 0.029), but it did not correlate with eGFR, HbA1c, serum glucose level, duration of diabetes mellitus, systolic and diastolic blood pressures (*p*: >0.05).

Table III demonstrates the associations between demographic, clinical, and laboratory parameters and microalbuminuria in binary logistic regression analysis. In the multivariate analysis, eGFR and GGT status were found to be independent risk factors for microalbuminuria.

DISCUSSION

In this study, we found that serum GGT activity was significantly increased in patients with microalbuminuric diabetic patients compared with normoalbuminuric diabetic patients. We also found that there was a strong and significant correlation between serum GGT activity and albuminuria and high GGT status was an independent risk factor for microalbuminuria.

Increased urinary protein excretion is the earliest clinical manifestation of diabetic nephropathy (2). Studies in diabetic patients with microalbuminuria demonstrate both an increase in the number of large pores (limiting size-selectivity) and decreased staining for heparan sulfate (the major component of the charge barrier) (16-19). Microalbuminuria is a marker of endothelial dysfunction or generalized vasculopathy, which may lead to an atherogenic state (5,6), and endothelial dysfunction possibly precedes the development of microalbuminuria in patients with diabetes mellitus (7).

Oxidative stress resulting from increased production of reactive oxygen species caused by hyperglycemia plays an important role in the pathogenesis of complications of diabetes mellitus including nephropathy (20). GGT is an enzyme**,** which is localized in the cell membranes of many tissues**,** and acts as a mediator in the transmembrane transfer of glutathione. Recently, serum GGT has been proposed as a sensitive and reliable marker of oxidative stress (9). In addition, serum GGT levels have been shown to be associated with endothelial dysfunction in several disorders such as Behçet disease and chronic kidney disease (13,21). In the present study, the relationship between serum GGT level and microalbuminuria is probably a reflection of endothelial dysfunction and oxidative stress. However, we cannot assess oxidative stress and endothelial function. This was one of limitations of this study.

In the present study we found an association between serum GGT levels and age. Similarly, Daeppen et al. reported that GGT

Table II: Comparison of demographic, clinical, and biochemical parameters between the patient groups.

	Normoalbuminuric group (n: 51)	**Microalbuminuric group (n: 56)**	**p value**
Age (year)	57 ± 11	60 ± 10	0.124
Gender			0.208
Male (%)	17 (33.3)	24 (42.9)	
Female (%)	34 (66.7)	32 (57.1)	
Type of diabetes mellitus			0.448
Type 1 (%)	4 (7.8)	3 (5.4)	
Type 2 (%)	47 (92.2)	53 (94.6)	
Presence of hypertension (%)	24 (47.1)	41 (73.2)	0.005
Duration of diabetes mellitus (year)	5.0 (1.0-25.0)	7.5 (1.0-32.0)	0.144
Systolic blood pressure (mmHg)	130 (100-180)	140 (100-210)	0.063
Diastolic blood pressure (mmHg)	80 (60-120)	90 (70-120)	0.078
Use of ACEI or ARB (%)	19 (37.3)	34 (60.7)	0.013
Presence of coronary artery disease (%)	10 (19.6)	15 (26.8)	0.259
Smoking			0.867
Never (%)	45 (88.2)	51 (91.1)	
Active smoker (%)	4 (7.8)	3 (5.4)	
Ex-smoker (%)	2 (3.9)	2 (3.6)	
Serum GGT level (IU/L)	21 (8-77)	27 (4-315)	0.011
GGT group			0.002
Low GGT group (%)	35 (66.7)	21 (37.5)	
High GGT group (%)	17 (33.3)	35 (62.5)	
Urinary albumin creatinine ratio	0.009 (0.001-0.029)	0.110 (0.031-0.300)	<0.001
HbA1c (%)	6.4 (4.5-10.7)	6.5 (4.5-12.5)	0.297
Serum glucose (mg/dL)	124 (86-338)	139 (67-467)	0.546
Triglyceride (mg/dL)	140 (63-360)	152 (58-1105)	0.251
Total cholesterol (mg/dL)	177 ± 38	202 ± 37	0.001
Low-density lipoprotein cholesterol (mg/dL)	100 ± 31	128 ± 32	<0.001
High-density lipoprotein cholesterol (mg/dL)	44 ± 8	42 ± 10	0.433
Use of statin (%)	10 (19.6)	11 (19.6)	0.595
Presence of dyslipidemia (%)	17 (33.3)	30 (53.6)	0.118
Alanine aminotransferase (IU/L)	21 (10-150)	24 (10-114)	0.182
Alkaline phosphatase (IU/L)	83 (36-169)	83 (48-304)	0.955
Serum albumin (g/dL)	4.1 ± 0.3	4.1 ± 0.4	0.714
eGFR (ml/min)	93 ± 29	73 ± 24	<0.001

ACEI: Angiotensin converting enzyme inhibitor, **ARB:** Angiotensin II receptor blocker, **GGT:** Gamma glutamyl transferase, **eGFR:** Estimated glomerular filtration rate

is positively related to age and this relationship was independent of alcohol consumption (22).

Mogensen has divided 5 stages in the development of renal changes and lesions in insulin-dependent diabetes mellitus (23). In the first two stages (i.e. renal hyperfunction and normoalbuminuria, respectively), albumin excretion is normal and GFR is elevated or high normal. In the third stage (i.e. incipient diabetic nephropathy), there is microalbuminuria and GFR is still at supranormal values. Blood pressure starts to increase; it increases approximately 3 mmHg per year if

Table III: The associations between demographic, clinical, and laboratory parameters and microalbuminuria (by binary logistic regression analysis).

Parameter	β	P value
Age	0.007	0.815
Gender (male or female)	0.069	0.899
Duration of diabetes mellitus	0.033	0.343
Presence of hypertension (no or yes)	1.089	0.207
Use of ACEI **or** ARB (no or yes)	0.666	0.444
GGT status (low or high)	1.155	0.037
Presence of dyslipidemia (no or yes)	0.699	0.203
eGFR	-0.053	<0.001

ACEI: Angiotensin converting enzyme inhibitor, **ARB:** Angiotensin II receptor blocker, **GGT:** Gamma glutamyl transferase, **eGFR:** Estimated glomerular filtration rate

untreated. For reasons that are not understood, the degree of albuminuria is not necessarily related to disease progression in patients with diabetic nephropathy (24,25). In the present study, we found that mean eGFR values were 93 ± 29 ml/min and 73 ± 24 ml/min in patients with normoalbuminuria and those with microalbuminuria, respectively. In both groups, eGFR values were lower according to expected values in diabetic nephropathy stages defined by Mogensen. This likely reflects the situation mentioned above, in which the degree of albuminuria is not necessarily related to disease progression in diabetic nephropathy. On the other hand, eGFR values were significantly lower in patients with microalbuminuria than in those with normoalbuminuria. This finding was compatible with natural history of type 1 diabetic nephropathy defined by Mogensen. In addition, hypertension was frequent in microalbuminuric group compared to normoalbuminuric group. This observation also was compatible with the natural history of type 1 diabetic nephropathy defined by Mogensen.

The role of renin-angiotensin system (RAS) blockade in normotensive, normoalbuminuric diabetic patients for the primary prevention of diabetic nephropathy is controversial. For diabetic patients with microalbuminuria or overt diabetic nephropathy, the optimal therapeutic approach to reduce the rate of progression of nephropathy and to minimize the risk for cardiovascular events involves aggressive management of hypertension with a RAS blocker combined with management of other risk factors including dyslipidemia (26-29). Similarly, in the present study, RAS blockade (use of ACEI or ARB) was frequent in microalbuminuric group compared to normoalbuminuric group.

There are several limitations of this study. Firstly, the study was cross-sectional and the potential causal relationship between serum GGT levels and microalbuminuria cannot be concluded. Secondly, as mentioned above, we did not assess oxidative stress and endothelial function. Thirdly, number of patients in the study was relatively low. To better clarify that issue, further studies with great numbers are warranted.

In conclusion, the results of the present study suggest that serum GGT levels are significantly higher in microalbuminuric diabetic patients. The underlying cause of this finding should be elucidated.

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