



Evaluation of Serum Gamma Glutamyl Transferase Levels in Diabetic Patients With and Without Retinopathy

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Abstract

Background: Gamma glutamyl transferase (GGT) is a liver enzyme that is involved in oxidative stress. The association between GGT levels and diabetes complications such as microalbuminuria, retinopathy, and peripheral polyneuropathy is a challenging subject.

Objectives: In this study we compared GGT levels in orally treated DM type 2 patients with and without retinopathy.

Methods: In this cross-sectional study that was done between the years of 2011 and 2012, 208 patients with Type 2 DM, aged 30 - 86 years old, who had received oral agents, and referred to the Endocrine clinic of Emam Khomeini hospital of Urmia city were enrolled. In all patients blood pressure, body mass index, and biochemical tests including fasting blood sugar (FBS) and GGT levels were measured and an ophthalmologic exam was done.

Results: From 208 patients with Type 2 DM, 26 subjects (12.5%) had diabetic retinopathy; however, 182 subjects (87.5%) did not have it. Both systolic and diastolic blood pressures were significantly higher in DM 2 patients with retinopathy than those without retinopathy (P values = 0.003 and 0.022, respectively). The mean of GGT level significantly increased in diabetic patients with retinopathy compared those DM 2 patients who did not have retinopathy (P value < 0.001). Prevalence of GGT levels greater than 45 U/l was 61.5% (n = 16) and 10.4% (n = 19) in diabetic patients with and without retinopathy, respectively (P value < 0.001).

Conclusions: We suggest that diabetic retinopathy might have an association with higher GGT levels.

Keywords: Gamma Glutamyl Transferase, Type 2 Diabetes Mellitus, Diabetic Retinopathy

1. Background

Diabetes mellitus (DM) is a debilitating disease with many health problems. It has been estimated that DM patients' population will increase to 380 million by 2025 (1). Diabetic retinopathy (DR) is one of the most frequent causes of blindness and other eye diseases in the world (2). A variety of mechanisms such as polyol pathway and increased sorbitol concentration, increased advanced glycation endproducts (AGEs) levels, overexpression of growth factors, oxidative stress, and inflammatory process have been proposed in the pathogenesis of DR and other chronic complications of DM (1). Oxidative stress has a main role in the development of DM related retinopathy, nephropathy, neuropathy, and cardiovascular dysfunction, although its exact mechanism is not well known (2, 3). Reactive oxygen species (ROS) plays a contributory role in DR by metalloproteinase -2 (MMP-2) ac-

tivation that promotes mitochondrial damage, apoptosis, and retinal endothelial dysfunction (1). Gamma glutamyl transferase (GGT), which is mainly produced in the liver, has been known as a marker of oxidative stress (OS) system (4-6). Some studies have revealed that higher GGT level is an earlier marker of diabetes development (6-9). It is also suggested that increased GGT levels is associated with metabolic syndrome and hepatic fat accumulation (6, 9-11). The association of GGT levels with BP, BMI, and acute coronary syndrome has been shown recently (4, 10, 12, 13).

Arkkila et al., in 2001, showed the association between GGT levels and DM complications including peripheral neuropathy and DR in DM Type 1 patients (14).

In a study by Cho and colleagues, in 2009, the relationship between high serum levels of Gamma glutamyl transferase (GGT) enzyme and diabetic peripheral polyneuropathy (DPP) has been detected (15).

2. Objectives

The relationship between serum GGT and DR in orally treated Type 2 DM subjects was assessed in this study.

3. Methods

In a cross-sectional study, 208 patients with Type 2 DM aged 30-86 years old, who had taken oral antidiabetic agents (either sulfonylureas, Metformin, Pioglitazone and Acarbose or a combination of them), and referred to Endocrine clinic of Emam Khomeini hospital of Urmia city were enrolled. The study was done between the years of 2011 and 2012 after approval by the Urmia University of medical sciences ethic committee.

Patients who had elevated liver enzymes more than three folds above the upper normal range, viral or autoimmune hepatitis, cirrhosis, untreated thyroid disorders, renal failure, alcohol consumption, osteomyelitis, or active foot ulcer were excluded.

Written informed consent was obtained from all subjects and blood pressure (BP), body weight, height, and body mass index (BMI) were recorded. Fasting venous blood samples were drawn from all subjects at the morning hours for measuring fasting blood sugar (FBS) and GGT levels. FBS and GGT were measured by enzymatic method and photometric method, respectively (Pars Azmun kite, Tehran, Iran). Normal range of GGT was considered up to 45 IU/l.

All patients were examined by an ophthalmologist for evaluation of the presence of diabetic retinopathy including background, preproliferative, and proliferative forms.

Each of the patients' information, including laboratory tests results and ophthalmologic exam, were recorded separately on a questionnaire. Data were analyzed by t-test, Mann-Whitney U test, and Chi-square and Pearson Correlation tests using the SPSS version 16. The level of statistical significance was considered as $P < 0.05$.

4. Results

The average age of patients was 55.7 ± 9.8 years. From 208 patients with Type 2 DM, 67.3% ($n = 140$) and 32.7% ($n = 68$) were female and male, respectively. A total of 26 patients (12.5%) had retinopathy, however, 182 patients (87.5%) did not have retinopathy in the eye exam.

The demographic characteristics and biochemical parameters of study groups are demonstrated in [Table 1](#).

As showed in [Table 1](#), the mean BMI did not have any significant difference between two groups of patients with and without DR (P value = 0.728). Diabetic patients with retinal involvement had higher blood pressure (both

systolic and diastolic) in comparison with other group ($P = 0.003$ and $P = 0.022$ respectively). The mean GGT levels were significantly higher in diabetic patients with retinopathy than those with normal retinal exam (P value < 0.001). The frequency of GGT levels greater than 45 IU/l was 61.5% in diabetic patients with retinopathy that was significantly higher than retinopathy negative patients (10.4%), (P value < 0.001).

There was no statistically significant relationship between age and GGT values ($r = 0.047$, p value = 0.497).

The mean serum GGT level was 32.4 ± 16.4 in men ($n = 68$) and 31.1 ± 15.4 IU/l in women ($n = 140$); there was no significant difference between men and women in this regard (P value = 0.55).

A total of 20.6% ($n = 14$) of the men and 15% ($n = 21$) of the women had GGT levels above 45 IU/l. In this regard, no statistically significant difference was observed between the two groups. (P value = 0.312).

5. Discussion

Serum GGT has been denoted as a novel biomarker of chronic inflammation and OS in some researches (16). OS has a role in the development of chronic complications of DM (6, 7, 9, 14, 15, 17).

The result of the present study was in favor of higher GGT levels in Type 2 diabetic patients with retinopathy.

Various studies showed that GGT levels may be a predictor of diabetes mellitus risk and its chronic complications (4, 6-10, 15). Relationship between GGT levels with BMI, BP, microalbuminuria, diabetic peripheral neuropathy, metabolic syndrome, and acute coronary syndromes has been shown previously (6, 7, 9, 10, 12, 13, 15, 18).

High GGT level causes excess fat accumulation in the liver, which reduces insulin sensitivity and contributes to hyperinsulinemia and metabolic syndrome (10, 12).

Meisinger et al., in 2005, during a 14-year longitudinal study, concluded that GGT is a valuable predictor of Type 2 diabetes incidence in both the male and female gender (9).

A retrospective cohort study had been done by Kim et al., (2002 to 2006), on 1717 Korean men without impaired fasting glucose (IFG) or Type 2 diabetes. They monitored FBS levels annually and identified 570 subjects with IFG and 50 subjects with diabetes incidence. There was a dose dependent correlation between higher GGT levels (even within its normal ranges) and IFG and/or DM type 2 incidences in their study (8).

Kotani et al., studied the relationship between GGT levels and systolic blood pressure in diabetic patients and healthy controls and they found a significant association between high levels of GGT and increased systolic blood

Table 1. Demographic Characteristics and Biochemical Parameters of Type 2 Diabetic Patients Based on the Presence and Absence of Retinopathy

Parameter	Patients With Retinopathy (n = 26)	Patients Without Retinopathy (n = 182)	P Value
Age, y	62.8 ± 9.5	54.7 ± 9.5	< 0.001
Male, %	10 (38.5)	58 (31.9)	0.509
BMI, kg/m ²	29.6 ± 4.9	30.0 ± 5.2	0.728
GGT level, U/l	44.3 ± 20.2	29.7 ± 14.2	< 0.001
GGT > 45 U/l, %	16(61.5)	19(10.4)	< 0.001
FBS, mg/dl	166.7 ± 60.9	158.1 ± 61.3	0.504
SBP, mm Hg	149.8 ± 26.7	137.9 ± 17.8	0.003
DBP, mm Hg	90.2 ± 12.7	85.1 ± 10.2	0.022

pressure in both diabetic and non-diabetic participants (4).

Lee and colleagues, in a 4-year follow-up study, on 4088 healthy men, demonstrated that elevated GGT levels has a significant correlation with diabetes development in a dose dependent manner (7).

Based on the Kasapoglu et al., study, serum GGT, as a pro-oxidant, also involved in the process of carotid and coronary arteries atherosclerosis and its levels, even in normal limits, can predict the metabolic syndrome and cardiovascular disease incidence (13).

Emiroglu et al., investigated GGT levels in 219 non-diabetic and Type 2 diabetic patients with acute coronary syndrome and 51 control subjects. They showed higher GGT levels in ACS cases compared with the control group (without any significant differences between diabetic and nondiabetic subjects). They suggested that GGT plays an important role in atherogenesis independently from Type 2 DM. They also explained that GGT role in inflammatory process and coronary atherosclerosis is resulted from its pro-oxidant effect and oxidation of LDL particles (13).

The findings of the Lee et al., prospective cohort study was in favor of a direct association between elevated GGT levels and Type 2 DM development independently from BMI and life style (6).

Oxidative stress is involved in the pathogenesis of various metabolic disorders such as insulin resistance and diabetes mellitus (11). Its role in the nerve damage in diabetic patients with neuropathy has been suggested (15).

GGT level is a biomarker of liver and systemic oxidative stress, however, the exact mechanism by which GGT contributes in OS system has not been well explained. From previous studies, it seems that GGT plays a contradictory role inside and outside the cells (19, 20). GGT causes Glutathione degradation and removal of gamma-glutamyl portion outside of the cells and released materials are transported into the cells and is used to produce glutathione in the cells. By increasing intracellular glu-

tathione content, which acts as an antioxidant inside the cells, GGT may be a defensive mechanism of body to OS (19). In addition to glutathione degradation and pro-oxidant properties of GGT outside the cells, it may play directly in the reactive oxygen species production (5, 13, 16).

In a study by Arkkila et al., in Finland, among 28 male patients with Type 1 diabetes, with an average duration of disease 25.2 ± 9.7 years, subjects with diabetic retinal involvement had higher levels of GGT compared with patients without diabetic retinopathy, which is consistent with the results of our study. In addition, they found that higher levels of GGT are associated with the severity of retinal involvement. Furthermore, Type 1 DM patients with peripheral neuropathy had higher levels of ALT and GGT than those without it (14).

In another study conducted in Central Africa in 2010, Type 2 diabetic patients with retinopathy compared to diabetic patients without retinopathy and non-diabetic patients had significantly higher levels of GGT levels as a marker of OS, which is in agreement with our study results (21).

Cho et al., in their study on 90 patients with Type 2 diabetes in 2009, reported higher levels of GGT in people with distal peripheral neuropathy than those without it (15).

Significant correlation between serum GGT levels and retinopathy in Type 2 diabetic patients in our study support the findings of previous studies, which have suggested measurement of serum GGT as a valuable test for predicting microvascular complications of diabetes, such as peripheral neuropathy and retinopathy (14, 15).

Based on our results, serum GGT levels are significantly higher in DM patients with retinopathy compared to DM patients without retinopathy. It can be useful in practice to identify DM subjects who are at risk of retinopathy. According to our results it seems reasonable to refer DM Type 2 patients with elevated GGT levels for careful ophthalmologic exam.

The main limitation of our study is a small sample size,

especially in diabetic patients with retinopathy. Future prospective cohorts with a greater sample size is recommended for better clarifying the correlation between GGT concentration and risk of DR and other chronic diabetes mellitus complications. We also suggest diabetologists to do more researches for investigating the correlation between GGT levels and degree of retinal involvement.

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