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*Original Article*

# Relationship between gamma-glutamyl transferase and glucose intolerance in first degree relatives of type 2 diabetics patients

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## Abstract

**BACKGROUND:** Considering that serum gamma-glutamyl transferase (GGT) activity could reflect several different processes relevant to diabetes pathogenesis and the increasing rate of type 2 diabetes worldwide, the aim of this study was to assess the association between serum GGT concentrations and glucose intolerance, in the first-degree relatives (FDR) of type 2 diabetic patients.

**METHODS:** In this descriptive study, 30-80 years old, non diabetic FDRs of type 2 diabetic patients were studied. Serum GGT was measured by enzymatic photometry method in all studied population. The relationship between GGT and glucose intolerance status (normal, prediabetic and diabetics) was evaluated.

**RESULTS:** During this study 551 non-diabetic FDRs of type 2 diabetic patients were studied. Mean of GGT was 25.3 ± 12.1 IU/L. According to glucose tolerance test, 153 were normal and 217 and 181 were diabetic and prediabetic respectively. Mean of GGT in normal, prediabetic and diabetic patients was 23.5 ± 15.9 IU/L, 29.1 ± 28.1 IU/L and 30.9 ± 24.8 IU/L respectively ($p = 0.000$). The proportion of prediabetic and diabetic patients was higher in higher quartile of GGT and there was a significant correlation between GGT and BMI, HbA1c, FPG, cholesterol, LDL-C, and triglyceride ($p < 0.05$). There was a significant relation between GGT and area under the curve (AUC) of oral glucose tolerance test ($p = 0.00$).

**CONCLUSIONS:** Measurement of GGT in FDRs of type 2 diabetic patients may be useful in assessing the risk of diabetes; those with chronically high levels of GGT should be considered as high risk group for diabetes.

**KEYWORDS:** Gamma-Glutamyltransferase, Glucose Intolerance, Diabetes Mellitus, Type 2.

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Serum gamma-glutamyl transferase (GGT) is an ectoplasmic enzyme responsible for the extracellular catabolism of glutathione, which is synthesized in epithelial cells of the intrahepatic duct. It distributed in different cells with various secretory or absorptive activities.[1] GGT has an important role in glutathione homeostasis by initiating the breakdown of extracellular glutathione and turnover of vascular glutathione.[2-4] Considering the antioxidant activity of glutathione, increased level of GGT may be linked to greater oxidative stress. Increased oxidative stress has been implicated in insulin resistance by promoting ß-cell dysfunction and reducing insulin action.[5,6] Therefore, serum GGT activity could reflect several different processes relevant to diabetes pathogenesis.

Many epidemiological studies, have demonstrated high rates of elevated GGT levels among diabetic patients over past 40 years.[1] The association between serum GGT and poor glycemic state was also documented in the 1980s.[7] Recent prospective studies, have indi-

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cated that baseline serum GGT activity predicts occurrence of future diabetes, stroke and cardiovascular diseases[8-19] and within reference interval, it strongly predicted incident type 2 diabetes.[10,13-18] However, not all studies support this assumption.[20]

In a recent study, among general population, in Tehran, Tohidi et al have investigated the association of GGT with incident type 2 diabetes. According to their findings, GGT was not independently associated with diabetes, but after adjustments for family history, anthropometric factors and blood pressure, it had relationship with type 2 diabetes.[21]

Considering the increasing rate of type 2 diabetes worldwide, in all ages, sexes, and race/ethnic groups,[22] we designed this study to investigate the association between serum GGT concentration and glucose intolerance, in the first-degree relatives (FDR) of type 2 diabetic patients. However, no studies have been performed to date on these populations.

## Methods

In this cohort study, non diabetic first-degree relatives of type 2 diabetic patients who were 30-80 years old and referred to Endocrine and Metabolic Research Center during Diabetes Prevention Project (DPP) study were enrolled (1893 FDRs of type 2 diabetic patients). For recruiting samples, we asked first-degree relatives of type 2 diabetic patients aged 30-80 years old to participate in the study by announcing through mass media. Informed consent was obtained from all studied subjects. Characteristics of studied subjects (demographic, familial history, past medical history …) were obtained using standard questionnaire.

The exclusion criteria were having a history of thyroid, renal, or hepatic disease, known diabetes, myocardial infarction, acute or chronic inflammatory disease or taking any medications.

### *Physical Examinations*

All studied subjects were examined by physicians. Anthropometric measurements were performed by trained nurses. Height and weight was measured in standing position, with light clothing and bare foot using Seca measuring device.

### *Laboratory Measurements*

In order to perform oral glucose tolerance test (OGTT), participants recommended using unrestricted diet with more than 150 g of carbohydrate daily and doing usual physical activities at least 3 days before laboratory tests. They recommended to fasting at least 10 hours before lab tests and not using any drug that may affect the metabolism of carbohydrate. After an overnight fasting, a 75 g OGTT was performed. Plasma glucose was measured using an enzymatic glucose oxidase technique using Chem-Enzyme kit (Tehran-Iran). Plasma lipids including cholesterol, HDL-C and triglyceride (TG) were measured using enzymatic method by Liasys auto-analyzer (Italy). Gamma-glutamyl transferase (GGT) was analyzed by enzymatic photometry method using Pars-Azmoon kit (Tehran-Iran).

Inter-assay coefficients of variations (CVs) were 1.25 for TG, 1.2 for cholesterol, 1.25% for glucose and 2.5% for GGT. The corresponding intra-assay CVs were 1.97, 1.6, 2.2 and 1.5 respectively.

HbA1c was measured by ion exchange chromatography with DS5 set. LDL cholesterol was calculated using Friedwald formula.[23]

Glucose intolerance in studied subjects was classified as below based on 2003 ADA criteria.[24]

- Diabetic: FPG > 125 mg/dl (6.9 mmol/l) or 2h-PG > 199 mg/dl (11 mmol/l)
- IFG: 100 mg/dl (5.6 mmol/l) ≤ FPG ≤ 125 mg/dl (6.9 mmol/l) and 2h-PG < 140 mg/dl (17.8 mmol/l)
- IGT: FPG ≤ 100 mg/dl (5.6 mmol/l) and 140 mg/dl (7.8 mmol/l) ≤ 2h-PG ≤ 199 mg/dl (11 mmol/l)
- Normal glucose tolerance (NGT): FPG < 100 mg/dl (5.6 mmol/l) and 2h-PG < 140 mg/dl (7.8 mmol/l)

Patients with IFG and IGT considered as prediabetic.

**Table 1.** Baseline characteristics of first-degree relatives of type 2 diabetic patients (n = 551)

| | Mean ± SD | Median (range) |
|---|---|---|
| Age (years) | 49.1 ± 10.1 | 48 (30-80) |
| BMI (kg/m$^2$) | 28.9 ± 4.6 | 28.5 (17.2-46.4) |
| FPG (mg/dl) | 113.8 ± 43.2 | 109 (69-449) |
| HbA1c (%) | 6.5 ± 1.8 | 5.6 (4-12.5) |
| Cholesterol (mg/dl) | 96.9 ± 38.5 | 192 (116-385) |
| HDL-C (mg/dl) | 48.1 ± 12.9 | 47 (22-90) |
| LDL-C (mg/dl) | 116.1 ± 31.6 | 113.6 (34.8-279.2) |
| Triglyceride (mg/dl) | 162.5 ± 88.5 | 140 (54-845) |
| GGT* (U/L) | 25.3 ± 12.1 | 21.9 (7.6-73.3) |

***** gamma-glutamyltransferase

***Statistical Analysis***

Statistical analysis was performed using SPSS software version 13. Log transformation was used in order to reduce skewness. Otherwise, for variables which were not normally distributed, median was presented. For all other variables with normal distribution, data were presented as mean ± SD.

Mean and/or median of studied variables, between groups were compared using ANOVA, Kruskal-Wallis, Wilcoxon test (when appropriate) and Post hoc tests.

P values < 0.05 were considered statistically significant. We analyzed serum GGT levels as quartiles: lees than 16.5 U/L, 16.5-21.9 U/L, 22-30.5 U/L, and more than 30.5 U/L.

To compare the prognostic abilities of GGT on glucose tolerance, we plotted glucose intolerance status against the quartiles of GGT.

Area under the receiver operating characteristic curve (AUC) of the logistic regression model was used to determine the cutoff of GGT as a predictive value for type 2 diabetes.

## Results

551 non-diabetic first-degree relatives of type 2 diabetic patients aged 30-80 years old were studied. Baseline characteristics of all studied population are presented in table 1. Mean or median of studied variables in all studied population according to the GGT quartiles is presented in table 2.

From the studied population, 167 were men. Mean of GGT was 31.1 ± 13.2 and 22.7 ± 10.7 in men and women respectively (p < 0.001).

According to the ADA criteria, 153 out of 551 participants were normal and 217 and 181 were diabetic and prediabetic, respectively. Mean of GGT in normal, prediabetic and diabetic patients was 23.5 ± 15.9, 29.1 ± 28.1 and 30.9 ± 24.8 respectively (p < 0.001).

The proportion of normal, prediabetic and diabetic patients according to the quartiles of GGT is presented in figure 1.

The relation between GGT and area under the curve (AUC) of oral glucose tolerance test is presented in figure 2.

According to the results of GGT area under the receiver operating characteristic curve (AUC) of the logistic regression models, cutoff of GGT as a predictive value for type 2 diabetes was 14 U/L.

**Table 2.** Mean or median of studied variables in first-degree relatives of type 2 diabetic patients according to the gamma-glutamyl transferase quartiles (n = 551)

| | Q1 (< 16.5 ) | Q2 (16.5-21.9) | Q3 (22-30.5 ) | Q4 (> 30.5) | P value |
|---|---|---|---|---|---|
| Age (years) | 46.9 ± 10.2 | 47.5 ± 9.3 | 51.4 ± 10.7 | 50.6 ± 9.8 | p < 0.05 |
| BMI (kg/m$^2$) | 28.0 ± 4.8 | 28.9 ± 4.5 | 28.8 ± 4.0 | 30.0 ± 4.8 | p < 0.05 |
| FPG (mg/dl) | 100 (61-449) | 107.5 (78-376) | 116 (78-386) | 125 (68-425) | p < 0.05 |
| HbA1c (%) | 5.3 (4-10) | 5.6 (4.1-11.7) | 5.6 (4.4-11.6) | 5.9 (4.1-12.5) | p < 0.05 |
| Cholesterol (mg/dl) | 187.7 ± 30.8 | 193.9 ± 34.1 | 197.5 ± 42.3 | 208.8 ± 47.8 | p < 0.05 |
| HDL-C (mg/dl) | 51.3 ± 13.4 | 46.8 ± 12.6 | 47.1 ± 12.5 | 47.2 ± 12.9 | p < 0.05 |
| LDL-C (mg/dl) | 111.9 ± 27.0 | 116.8 ± 30.0 | 114.5 ± 33.2 | 121.3 ± 35.5 | 0.3 |
| Triglyceride (mg/dl) | 123.3 ± 65.4 | 152.3 ± 65.4 | 181.8 ± 107.7 | 193.2 ± 91.8 | p < 0.05 |

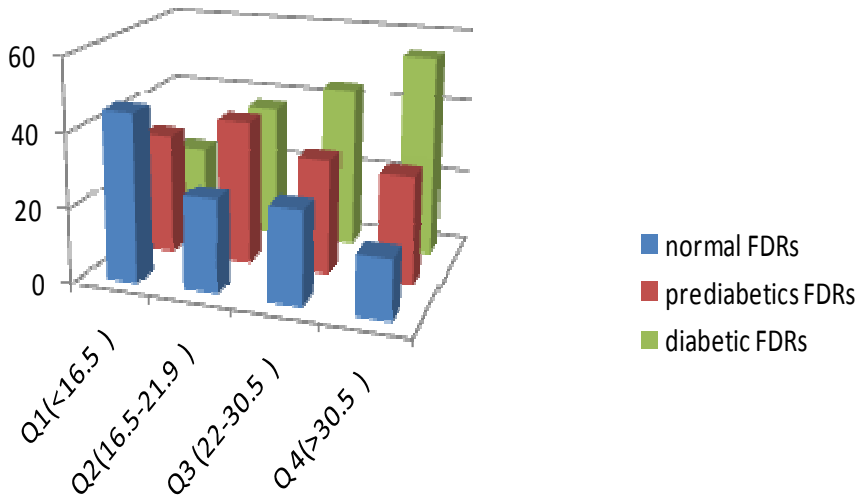


**Figure 1.** The proportion (%) of normal, prediabetic and diabetic patients according to quartiles of gamma-glutamyl transferase (U/L) ($p < 0.001$)

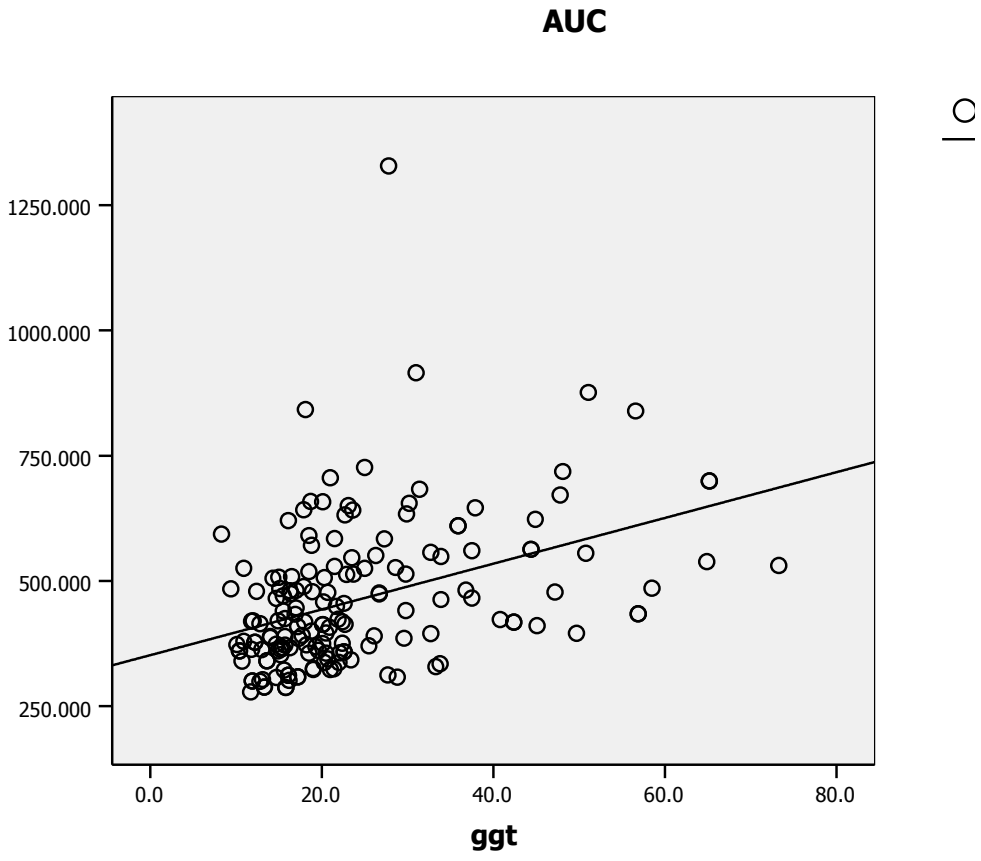


**Figure 2.** The relation between gamma-glutamyl transferase and AUC

There was a significant positive correlation between GGT and BMI, HbA1c, FPG, cholesterol, LDL-C, Triglyceride; but there was no relation with HDL-C. Age and sex were considered as control variables.

## Discussion

Although the association between serum levels of GGT and type 2 diabetes risk has been documented in several previous studies, to the best of our knowledge, this study was the first report to investigate this relationship in the FDRs of diabetic patients. The findings of our study have demonstrated that there was similar association between GGT and glucose intolerance in FDRs of diabetic patients and there was a relation between serum GGT and risk for development of IFG or type 2 diabetes. A GGT level of 14 U/L considered as cutoff point for predicting diabetes in FDRs of diabetic patients.

Mean of GGT in current study in all the studied population was 25.3 U/L; however, it was higher in prediabetic and diabetic FDRs.

In a population based study in Tehran, Tohidi et al have reported that median of GGT in subjects who did and did not develop diabetes after 3.5 years of follow-up was 16.9 U/L and 21.3 U/L, respectively. Results of current study were in line with the study of Tohidi et al.[21] Median of GGT in FDRs was similar to those subjects who developed diabetes after 3.5 years of follow-up in Tehran. This may be due to our studied population who were the first degree relatives of type 2 diabetes who are at higher risk for diabetes development.

The mean of GGT in Iranian healthy volunteer blood donors men was reported to be 20.52 U/L by Khedmat et al.[25]

Mean of GGT in this study was higher in men than in women, which was similar to the Hisayama study.[26]

These different results may be due to different methods of GGT measurements or differences in studied population. However, we could not ignore the importance of genetic and environmental sources of variations in GGT.[27]

Several studies have demonstrated the association between serum GGT level and diabetes. Some of them have indicated that GGT is a more powerful predictor of incident diabetes than other liver enzymes.[28] The results of these observations are different; our results are consistent with most[26,28-30] but not all[20,25] previous studies that evaluate the above mentioned association.

In the study of Khedmat et al in Iran, the prevalence of diabetes and also the presence of diabetes family history were not different regarding GGT quartile. Whereas, Tohidi et al have indicated that GGT was not associated with incident of type 2 diabetes, independent of classic risk factors; however, it predicted diabetes after adjustment for family history of diabetic patients as well as some factors including, body mass index, waist circumference, waist to hip ratio, systolic blood pressure and diastolic blood pressure. It lost its association with diabetes after further adjustment for other metabolic factors such as FPG, 2 hour postprandial glucose, triglyceride and HDL-C.[21]

Nakanishi et al investigated the association between serum GGT and risk of type 2 diabetes. The results of their investigation indicated that serum GGT may be an important predictor for developing type 2 diabetes mellitus and in accordance to our results, they concluded that the relative risk for impaired fasting glucose and type 2 diabetes increased as serum GGT increased.[29]

Recently, Sabanayagam et al have studied the association between serum GGT and diabetes mellitus in a nationally representative sample of US adults participating in the National Health and Nutrition Examination Survey (NHANES) (1999-2002), among 7,976 adults older than 20 years old; according to their results, serum GGT levels were found to be positively associated with diabetes mellitus.[30]

Kim et al in their study, in Korea, have shown that, the odds ratio of developing type 2 diabetes increased significantly with increasing GGT levels. In multiple logistic regression models adjusted for different variables, the highest quartile of GGT remained significantly associated with type 2 diabetes. They concluded that, increased serum GGT is independent and also additive risk factor for the development of diabetes in subjects without fatty liver or hepatic dysfunction.[28]

Doi et al in Japan, have studied the relationship between liver enzymes and the development of diabetes in a general Japanese population. Their findings suggest that serum GGT concentration consider as a strong predictor of diabetes in the general population, independent of other known risk factors.[26]

There was a significant correlation between studied variables in our study and GGT, especially in higher quartile of GGT. The findings were in line with the results of Kim et al study.[28]

The limitations of the current study are that, the study was a cross-sectional study which limits making causal inferences in the association between serum GGT and glucose intolerance. In addition, GGT data were based on a single measurement which consequently limits the precision of the elevated GGT estimates and finally it seems that our results would be more conclusive if the sample size was larger.

## Conclusions

Taken together, in spite of these limitations, the findings of this study could have practical and clinical implications in management of FDRs of diabetic patient. Measurement of GGT in this population may be useful in assessing the risk of type 2 diabetes and FDRs with chronically high levels of GGT (> 14) should be considered as high risk group for diabetes.

## Conflict of Interests

Authors have no conflict of interests.

## Authors' Contributions

All authors have contributed in designing of the study. ZP collected the data. SaH, SiH and PA did the analysis and interpretation and assisted in preparation of the manuscript. MA served as a supervisor. All authors have read and approved the content of the manuscript.

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