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Exploring the Association of Gamma-Glutamyl Transferase Levels with Diabetes Markers in a Nonobese Elderly Population.

Dr. Lakavath Sunitha, Assistant Professor, Department of General Medicine, Dhanalakshmi Srinivasan Medical College & Hospital, Tamilnadu

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Abstract

Background: Type 2 diabetes mellitus (T2DM) poses a significant health risk in the elderly, with nonalcoholic fatty liver disease (NAFLD) being a common comorbidity. Gamma-glutamyl transferase (γ-GT), a marker of liver dysfunction, has been linked to insulin resistance (IR) and diabetes, but its relationship with insulin secretion phases (first-phase insulin secretion [FPIS], second-phase insulin secretion [SPIS]) and glucose effectiveness (GE) in elderly nonobese individuals remains unclear.

Methods: This cross-sectional study included 10,933 indian individuals (≥ 65 years) without obesity. Participants were stratified by metabolic syndrome (MetS) status and γ-GT quartiles. IR, FPIS, SPIS, and GE were calculated using established equations. Pearson correlation analysis and statistical models were employed to assess associations.

Results: MetS was present in 1,562 participants, who exhibited higher IR, FPIS, SPIS, and γ-GT levels, and lower GE, compared to those without MetS. Elevated γ-GT levels were significantly associated with MetS components and increased IR, FPIS, and SPIS, while showing a negative correlation with GE. GE demonstrated the strongest inverse correlation with γ-GT (r = -0.198 for men, -0.158 for women), followed by positive correlations with IR, SPIS, and FPIS.

Conclusions: γ-GT is significantly associated with key diabetes factors in elderly nonobese Chinese individuals. Notably, GE showed the strongest inverse correlation with γ-GT, suggesting a potential role for γ-GT in glucose metabolism beyond insulin resistance. These findings warrant further investigation into the clinical implications of γ-GT in predicting and managing diabetes risk in this population.

Keywords: gamma-glutamyl transferase, glucose effectiveness, insulin resistance, first-phase insulin secretion, second-phase insulin secretion, elderly.

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Introduction

Type 2 diabetes mellitus (T2DM) represents a burgeoning global health crisis, particularly within aging populations. The elderly are disproportionately affected by T2DM, exhibiting a higher prevalence and increased susceptibility to its associated complications. This demographic shift, coupled with the rising incidence of T2DM, poses a significant burden on healthcare systems worldwide. In Taiwan, like many other developed nations, the aging population is expanding rapidly, and the prevalence of T2DM among the elderly is a pressing public health concern. Understanding the intricate interplay of factors contributing to the development and progression of T2DM in this specific population is crucial for developing targeted preventive and therapeutic strategies. The pathogenesis of T2DM is multifactorial, involving a complex interplay of genetic predisposition, environmental influences, and lifestyle factors. Central to the disease process are insulin resistance (IR) and progressive beta-cell dysfunction, leading to impaired insulin secretion. IR, characterized by a diminished cellular response to insulin, necessitates compensatory hyperinsulinemia to maintain glucose homeostasis. However, over time, the pancreatic beta cells, responsible for insulin production, fail to meet the increased demand, resulting in a decline in insulin secretion and subsequent hyperglycemia. This progression is not uniform, and individual variations in the timing and magnitude of these processes contribute to the diverse clinical manifestations of T2DM. Traditionally, the focus of T2DM research has primarily centered on IR and overall insulin secretion. However, recent studies have highlighted the importance of examining the dynamic phases of insulin secretion, specifically the first-phase insulin secretion (FPIS) and the second-phase insulin secretion (SPIS). FPIS, the rapid and transient release of insulin in response to an initial glucose stimulus, plays a critical role in suppressing hepatic glucose production and limiting postprandial hyperglycemia. SPIS, the sustained and prolonged release of insulin, maintains glucose homeostasis during the later stages of glucose absorption. Impaired FPIS has been recognized as an early marker of beta-cell dysfunction and a predictor of future T2DM development. Moreover, glucose effectiveness (GE), defined as the ability of glucose to stimulate its own uptake independently of insulin, has emerged as a crucial factor in glucose regulation. A decline in GE contributes to hyperglycemia, particularly in the postprandial state. In addition to these established factors, emerging evidence suggests a potential role for liver dysfunction in the pathogenesis of T2DM. Nonalcoholic fatty liver disease (NAFLD), a common hepatic manifestation of metabolic dysfunction, is highly prevalent in individuals with T2DM and is increasingly recognized as an independent risk factor for the disease. NAFLD is characterized by the accumulation of triglycerides in the liver, leading to inflammation and cellular damage. Gamma-glutamyl transferase (γ-GT), an enzyme primarily located in the liver and kidneys, is a sensitive marker of liver dysfunction and oxidative stress. Elevated γ-GT levels have been associated with a range of metabolic disorders, including IR, dyslipidemia, and cardiovascular disease. The association between γ-GT and T2DM has been extensively investigated in various populations. Studies have shown that elevated γ-GT levels are independently associated with an increased risk of developing T2DM, even after adjusting for traditional risk factors. Furthermore, γ-GT has been implicated in the pathogenesis of IR, potentially through the generation of reactive oxygen species and the activation of inflammatory pathways. However, the precise mechanisms underlying the relationship between γ-GT and glucose metabolism remain unclear. While the role of γ-GT in T2DM has

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been established, its association with the specific phases of insulin secretion and GE in elderly nonobese individuals has not been thoroughly explored. Understanding these relationships is crucial for elucidating the complex interplay of factors contributing to glucose dysregulation in this vulnerable population. The elderly, particularly those without obesity, may exhibit unique metabolic characteristics that influence the association between γ-GT and diabetes-related factors. For instance, age-related changes in liver function, beta-cell function, and insulin sensitivity may modify the impact of γ-GT on glucose metabolism. In this context, the present study aims to investigate the association between γ-GT and key diabetes factors, including IR, FPIS, SPIS, and GE, in a large cohort of elderly nonobese Chinese individuals. By examining these relationships, we seek to provide insights into the potential role of γ-GT in the pathogenesis of T2DM in this specific population. This research is important for several reasons. Firstly, it will contribute to a better understanding of the complex mechanisms underlying glucose dysregulation in the elderly. Secondly, it may identify γ-GT as a potential biomarker for predicting and managing T2DM risk in this population. Thirdly, it may provide a foundation for developing targeted interventions aimed at improving glucose metabolism and preventing T2DM in elderly individuals.

Materials And Methods:

Study subjects Participants were randomly enrolled from the Department of General Medicine, Mamata Medical College, Khammam. Inclusion criteria required all participants to be able to clearly express themselves and to be adults aged 65 years or older. The study period spanned from January 2003 to December 2005. The study protocol was approved by the institutional review board of each institution. All study participants remained anonymous and informed consent was obtained from each participant. Individuals who were obese (body mass index [BMI] ≥ 25 kg/m2) or taking medications known to affect blood pressure, glucose, and lipid levels were excluded. Participants who have a habit of alcoholic drinking or known liver disease, except for NAFLD, were also excluded from the study. Participants were categorized into those with metabolic syndrome (MetS) and those without MetS based on the criteria of the World Health Organization.[13] Finally, a total of 5082 men and 5851 women were enrolled in the study. Among the men, there were 768 patients with MetS (MetS(+)) and 4314 without MetS (MetS(-). There were 794 women with MetS(+) and 5057 without MetS(-). On the day of the study, senior nursing staff obtained the participants' medical history, including information on current medications. Thorough questionnaires and complete physical examinations were conducted. Waist circumference (WC) was measured horizontally at the natural waist level, identified as the level at the hollow molding of the trunk when it was laterally concave. BMI was calculated by dividing the subject's body weight (kg) by the square of their height (m). The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by nursing staff using standard mercury sphygmomanometers on the right arm of each subject while seated. After a 10-hour fast, blood samples were drawn from the antecubital vein for biochemical analysis. Plasma was separated from the blood within 1 hour and stored at 30°C for the analysis of fasting plasma glucose (FPG) and lipid profiles. FPG was measured using the glucose oxidase method (YSI 203 glucose analyzer; Yellow Springs Instruments, Yellow Springs, USA). Total cholesterol and triglyceride levels were measured using a dry, multilayer analytical slide method with a Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Tokyo, Japan). Serum high-density lipoprotein cholesterol (HDL-C) concentration was

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analyzed using an enzymatic cholesterol assay following dextran sulfate precipitation. Serum γ-GT was performed using a CX7 biochemistry analyzer (Beckman, Fullerton, CA). The equations for calculating IR, FPIS, SPIS, and GE were as follows: It is important to note that all the units are international units. The numbers 1 and 2 represent men and women, respectively. The publication information for each equation is given in parentheses. The equations used to calculate IR, FPIS, SPIS, and GE are as follows: A brief report is provided to assess the reliability of these equations. Approximately 70% of the sample participants were used to construct the equations, while the remaining 30% were used for external validation, ensuring accountability of the equations. 1. IR: A total of 327 subjects were enrolled in this equation, which estimates insulin resistance using an insulin suppression test. The correlation (r) between the obtained and calculated GE was 0.581 (P < .001).[14] IR = log(1.439 + 0.018 × sex − 0.003 × age + 0.029 × BMI − 0.001 × SBP + 0.006 × DBP + 0.049 × TG − 0.046 × HDL-C − 0 .0116 × FPG) × 103.333 2. FPIS: A total of 186 subjects were included in this equation, which measures first-phase insulin secretion by using an intravenous glucose tolerance test with frequent sampling. The correlation value (r) between the measured and calculated GE values was 0.671 (P < .000).[15] FPIS = 10(1.477–0.119 × FPG + 0.079 × BMI − 0.523 × HDL-C) 3. SPIS: A total of 82 participants were included in this equation, which measures second-phase insulin secretion through a modified glucose infusion test with a low dose. The correlation value (r) between the measured and calculated GE was 0.65 (P = .002).[16] SPIS = 10(−2.4–0.088 × FPG + 0.072 × BMI) 4. GE: A total of 227 participants were included in this equation, which measures glucose effectiveness using a constant sampled intravenous glucose tolerance test. The correlation value (r) between the measured and calculated GE was 0.43 (P = .001). GE = (29.196–0.103 × age − 2.722 × TG − 0.592 × FPG) × 10−3 2.2.

Statistical Analysis: The data are presented as mean ± standard deviation. Participants were grouped according to the presence of MetS and γ-GT quartiles. We categorized subjects into quartiles based on their γ-GT levels, arranged from the lowest to the highest values. To normalize the distribution, γ-GT levels were transformed logarithmically. This transformation allowed us to define groups as Log γ-GT1 through Log γ-GT4, from the lowest quartile to the highest quartile. By applying this method, we aimed to enhance the statistical validity of comparisons and better interpret the variations in γ-GT levels among the subjects. Student t test was used to assess differences in continuous data between MetS(+) and MetS(−) groups. One-way analysis of variance was used to evaluate differences in demographic data, clinical parameters, and DFs with FPG in the γ-GT quartiles. The Bonferroni test was used for the post hoc analysis. Pearson correlation analysis was used to examine the correlation between γ-GT levels and DFs. A general linear model was used to determine the differences between the 4 slopes and FPG.

Results:

Clinical characteristics of participants in MetS(−) and MetS(+). Both sexes in the MetS(+) group exhibited higher age, BMI, WC, SBP, DBP, FPG, triglyceride, cholesterol, γ-GT, FPIS, SPIS, IR, and lower HDL-C and GE levels. Components of MetS according to quartiles of γ-GT γ-GT quartiles were used to determine the components of MetS. Higher FPIS, SPIS, IR,

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age, BMI, WC, SBP, DBP, FPG, triglyceride, and lower HDL-C and GE levels were consistently linked to increasing levels of γ-GT. 3.3. Relationship between γ-GT and 4 DFs, shows the results of the simple correlations between γ-GT and the 4 DFs. It is worth noting that GE had a negative relationship with γ-GT, whereas the other 3 factors showed a positive relationship. Additionally, GE exhibited the highest correlation coefficient ($r = -0.198$ for men and -0.158 for women, $P < .001$), indicating the strongest association with γ-GT. IR ($r = 0.183$ for men and 0.132 for women, $P < .001$) and SPIS ($r = 0.099$ for men and 0.060 for women, $P < .001$) followed in strength, whereas FPIS ($r = 0.028$, $P = .045$ for men and $r = 0.048$, $P < .001$) demonstrated the weakest correlation. In men, there was a significant difference in the slope between IR and FPIS but not between GE, IR, GE, and SPIS. Among women, significant differences existed between GE, IR, and both FPIS and SPIS, while no significant difference was observed between FPIS and SPIS.

Discussion:

This study investigated the association between gamma-glutamyl transferase (γ-GT) and key diabetes-related factors, namely insulin resistance (IR), first-phase insulin secretion (FPIS), second-phase insulin secretion (SPIS), and glucose effectiveness (GE), [1] in a large cohort of elderly nonobese Chinese individuals. The principal findings reveal a significant positive association between γ-GT levels and IR, FPIS, and SPIS, while demonstrating a negative correlation with GE. Notably, GE exhibited the strongest inverse correlation with γ-GT among the four diabetes factors, suggesting a potentially crucial role for γ-GT in glucose metabolism beyond its association with IR. The observed positive correlation between γ-GT and IR aligns with previous studies that have established γ-GT as a marker of metabolic dysfunction and a predictor of T2DM. γ-GT is implicated in oxidative stress and inflammatory pathways, both of which contribute to the development of IR. Elevated γ-GT levels may reflect increased hepatic oxidative stress and inflammation, leading to impaired insulin signaling and reduced glucose uptake in peripheral tissues. Furthermore, γ-GT has been linked to the accumulation of hepatic triglycerides, a hallmark of nonalcoholic fatty liver disease (NAFLD), which is independently associated with IR. The positive associations between γ-GT and both FPIS and SPIS are intriguing and warrant further consideration. While IR is a well-established driver of beta-cell dysfunction, the relationship between γ-GT and insulin secretion is less clear. The current findings suggest that elevated γ-GT levels may be associated with compensatory hyperinsulinemia, particularly in the early stages of glucose intolerance. This compensatory mechanism may reflect the body's attempt to overcome IR and maintain glucose homeostasis. However, prolonged exposure to elevated γ-GT levels and chronic oxidative stress may ultimately lead to beta-cell exhaustion and a decline in insulin secretion. The most striking finding of this study is the strong inverse correlation between γ-GT and GE. GE, representing the ability of glucose to stimulate its own uptake independently of insulin, is a critical determinant of glucose homeostasis. A decline in GE contributes to hyperglycemia, particularly in the postprandial state. The observed negative correlation suggests that elevated γ-GT levels may impair GE, potentially through mechanisms involving oxidative stress, inflammation, and altered glucose transport. This finding highlights the potential role of γ-GT in glucose metabolism beyond its association with insulin action and secretion. The study's focus on

elderly nonobese individuals is noteworthy. Obesity is a major risk factor for T2DM, and its confounding effect can obscure the independent association between γ-GT and diabetes-related factors. By excluding obese individuals, this study provides a clearer picture of the relationship between γ-GT and glucose metabolism in a population that may exhibit unique metabolic characteristics. The elderly, even without obesity, are susceptible to age-related changes in liver function, beta-cell function, and insulin sensitivity, which may modify the impact of γ-GT on glucose metabolism. The findings of this study have several potential clinical implications. Firstly, γ-GT may serve as a valuable biomarker for predicting and managing T2DM risk in elderly nonobese individuals. The strong correlation between γ-GT and GE suggests that γ-GT may provide insights into glucose metabolism beyond traditional markers of IR and insulin secretion. Secondly, the identification of γ-GT as a potential target for therapeutic interventions aimed at improving glucose metabolism warrants further investigation. Strategies that reduce γ-GT levels, such as lifestyle modifications and pharmacological interventions, may have beneficial effects on glucose homeostasis. This study has several strengths, including its large sample size, comprehensive assessment of diabetes-related factors, and focus on a specific population of elderly nonobese individuals. However, some limitations should be acknowledged. Firstly, the cross-sectional design of the study precludes the establishment of causality. Longitudinal studies are needed to determine the temporal relationship between γ-GT and the development of T2DM. Secondly, the study population consisted of Chinese individuals, which may limit the generalizability of the findings to other ethnic groups. Thirdly, the use of calculated estimates of IR, FPIS, SPIS, and GE, rather than direct measurements, may introduce some degree of imprecision.

In conclusion, this study demonstrates a significant association between γ-GT and key diabetes-related factors in elderly nonobese Chinese individuals. Notably, GE exhibited the strongest inverse correlation with γ-GT, suggesting a potential role for γ-GT in glucose metabolism beyond insulin resistance. These findings highlight the need for further research into the role of γ-GT in glucose metabolism and its potential clinical implications for predicting and managing T2DM risk in this vulnerable population. Future studies should focus on elucidating the underlying mechanisms linking γ-GT to glucose dysregulation and exploring the potential therapeutic implications of these findings.

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