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Gamma-Glutamyl Transferase and the Risk of Type 2 Diabetes Mellitus: A Review

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Abstract

The relationship between gamma-glutamyl transferase (GGT) levels and risk factors for type 2 diabetes mellitus (T2DM) and the risk of incident T2DM was assessed using a narrative review of available evidence. Higher circulating levels of GGT are associated with an increased risk of type 2 diabetes mellitus, suggesting GGT as a risk predictor of T2DM. The incidence of type 2 diabetes and its association with GGT elevation could be explained by oxidative stress in cells followed by subclinical inflammation and fatty liver, leading to impaired insulin secretion and insulin resistance. A strong correlation is evident between BMI and GGT, in which hepatic steatosis and insulin resistance are proposed to be the intermediate connecting characteristics.

Keywords: Gamma-glutamyl transferase, Type 2 diabetes mellitus, Body mass index

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Introduction

The incidence of type 2 diabetes mellitus (T2DM) has increased along with its complications. Several studies have reported a strong correlation between the development of T2DM and gamma-glutamyl transferase (GGT). GGT acts as a non-specific index of liver dysfunction and a biomarker of excess alcohol consumption (1).

The identified risk factors for diabetes include high blood pressure, family history, body mass index (BMI), lipids and lipoproteins, age, and gender. The association of these factors with GGT has been investigated (2,3). Studies have suggested that the association of GGT with hepatic steatosis and insulin resistance affects the incidence of diabetes and hypertension (4-9). Elevated GGT levels in obese individuals suggest a strong association between obesity and hepatic insulin resistance (10). The relationship of serum GGT with obesity has been investigated by many studies using BMI as its indicator, and significant correlations of GGT with BMI have been reported in both diabetic and non-diabetic healthy individuals (3,11-13). Elevated serum GGT and its relationship with plasma insulin, obesity, and other cardiovascular risk factors may predict the development of T2DM. It has been suggested that the elevation of GGT in patients with diabetes is not caused by hyperglycemia but by pathologies associated with diabetes (3,14).

Gamma-glutamyl transferase

GGT is a glycoprotein (15) found in bacteria (16,17), plants (18,19), and animals, ranging from the nematode Ascaris suum (20) to humans. It consists of two proteins identified as a heavy chain and a light chain with a molecular weight of 68 kDa (15).

Humans carry seven GGT genes (21,22) located on chromosome 22q11 (23,24) and some pseudogenes with related sequences on chromosomes 18, 19, and 20. A functional and complete GGT protein is synthesized by only one of those seven or more genes (24). In humans, GGT is predominantly found in the liver and is elaborated by several other organs and extrahepatic tissues, including the lung, kidney, pancreas, spleen, brain, epididymis, seminal vesicles, lymphocytes, and fibroblasts (15,25-28).

GGT is a key enzyme that catalyzes the transfer of gamma-glutamyl groups between glutamyl peptides and common amino acids while metabolizing extracellular reduced glutathione (GSH) (15,25).

Functions of the GGT

GGT regulates the γ – glutamyl cycle (15), which is involved in the *de novo* synthesis of GSH, the main thiol intracellular antioxidant agent in mammalian cells (L-g-glutamyl-L-cysteinyl-glycine). Glutathione is the most abundant substrate for GGT (2,3).

This enzyme transfers the glutamyl moiety to an acceptor molecule, often an amino acid, by hydrolyzing the γ – glutamyl bond or glutathione-S-conjugates (29). The greatest activity of GGT has been found in tissues with transport function, such as the kidneys and biliary system. Therefore, it was suggested that GGT plays an important role in the transport of amino acids through a sequence of reactions forming the γ – glutamyl cycle and accounts for the availability of cysteine amino acids (3).

GGT deficiency in humans is rare; however, recessive inheritance is suggested by family histories. Although serum GGT elevation is associated with several diseases, there is limited evidence supporting the adverse effects of GGT deficiency in humans (30-33).

Measurement of GGT activity

Serum GGT is one of the main components of the liver function test, which is a common laboratory test with high accuracy and sensitivity. GGT is comparatively stable in vitro. It reflects liver dysfunction and is therefore considered an index of liver damage and alcohol consumption (2,3).

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GGT catalyzes the transfer of a glutamyl residue from one amino acid to an acceptor, usually another amino acid, through a gamma carboxylic acid linkage. Glutathione (gamma-glutamyl cysteinylglycine) is considered to be the most significant natural substrate for GGT. Several artificial substrates are also available for GGT to act upon. The acceptor molecules for the reaction catalyzed by GGT are amino acids or peptides, and glycine is known to be the most active and common acceptor molecule (3).

Several artificial substrates, including gamma-glutamyl-β -naphthylamide, gamma-glutamyl-p- nitroanilide, and gamma-glutamyl-3-carboxy-4-nitroanilide, have been developed for the convenient measurement of GGT. Continuous monitoring of the progression of the reaction is possible because the nitroanilides are chromogenic. Carboxylic acid is suggested as an alternative to gamma-glutamyl-p-nitroanilide that avoids limitations on solubility (3).

Kinetic methods of assaying the enzyme are the most satisfactory method, which is based on the work of Szasz G. (1969), who described the ability of the GGT enzyme to act on synthetic amides of glutamic acids such as gamma-glutamyl-β -naphthylamide, gamma-glutamyl-p-nitroanilide, and gamma-glutamyl-3-carboxy-4-nitroanilide (34). Kinetic methods monitor the release of p- nitroaniline from the substrate L-G-glutamyl-p-nitroanilide (3,25).

Reference intervals for the GGT

Reference intervals currently used for GGT in most laboratories are considered inappropriate. The reason is that several studies have shown increased mortality in patients even though their GGT levels are within the reference intervals (15).

Apparently normal healthy individuals were included to derive the reference interval for those who were negative for any chronic disease (15). However, special consideration should be taken when selecting normal subjects to establish reference ranges for serum GGT because of its effects on the development of chronic disease conditions such as cardiovascular and non-cardiovascular diseases (35,36). Therefore, screening individuals for unhealthy lifestyles, excessive alcohol consumption, hepatobiliary diseases including non-alcoholic fatty liver disease (NAFLD), chronic cardiovascular diseases, normal fasting plasma glucose concentration, HbA1c, blood pressure, waist circumference and lipids, long-term medication and with BMI < 25 kg/m^2 is required (15).

Establishing reference intervals at a national or international level would be desirable to lessen the drawbacks associated with patient identification and long-term follow-up whose GGT is measured in different laboratories (15).

Diabetes mellitus and insulin resistance

Diabetes mellitus (DM) is a heterogeneous group of multifactorial polygenic syndromes that result in elevated fasting blood glucose levels due to a relative or absolute insulin deficiency (9). Diabetes causes many complications such as; nerve damage, heart attacks, strokes, renal failure, adult blindness, and amputations.

There are three main types of DM:

- Type 1 diabetes mellitus or insulin-dependent or juvenile-onset diabetes mellitus
- Type 2 diabetes or non-insulin-dependent or adult-onset diabetes
- Gestational diabetes mellitus (37).

Patients with T2DM exhibit a combination of insulin resistance and dysfunction of β cells in the pancreas. Hyperglycemia, insulin resistance, and relative impairment of insulin secretion are characteristic features of type 2 diabetes (37). The inability of target tissues to respond to normal insulin concentrations leads to impaired insulin action, i.e., insulin resistance. It is required that β -cells in the pancreas must produce higher levels of insulin to preserve euglycemia. The maintenance of higher insulin secretion from β -cells is suppressed because of impaired insulin secretion over time, leading to impaired

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glucose tolerance and eventually T2DM. Insulin resistance and hyperinsulinemia are associated with other metabolic abnormalities besides hyperglycemia in T2DM (38).

Insulin Resistance

Insulin resistance is defined as the decreased capability of target tissues, such as the liver, adipose tissue, and muscle, to properly respond to normal or increased circulating insulin. This may be due to; uncontrolled hepatic glucose production and decreased uptake of glucose by adipose tissue and muscle. Patients who cannot compensate for insulin resistance due to increased insulin secretion are commonly elderly people and obese individuals who are physically inactive or pregnant women (3-5%) with gestational diabetes (37).

The most common cause of insulin resistance is obesity. However, most obese individuals with insulin resistance do not become diabetic. Non-diabetic, obese people without β cell functional defects can compensate for insulin resistance with increased insulin levels. According to evidence, insulin secretion in obese people is 2-3 times higher than that in lean individuals. The diminished effect of insulin hormones due to insulin resistance is compensated for by this higher insulin level. It will produce blood glucose levels in obese subjects similar to those of lean individuals. As insulin resistance decreases with weight loss and increases with weight gain, it reflects the importance of fat accumulation in the development of insulin resistance. Elevated levels of free fatty acids in obesity are a major factor in the development of insulin resistance (39). Manifestations of insulin resistance in obesity include impaired suppression of hepatic glucose output and decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle. Diminished insulin signaling in all three target tissues is suggested to result in these functional defects because of the downregulation of GLUT4, which is the major insulin-responsive glucose transporter. Moreover, a reduction is evident in the binding of insulin to its receptor, receptor phosphorylation, tyrosine kinase activity, and phosphorylation of insulin-receptor substrates (IRS) in both adipocytes and muscle. Insulin signaling molecules are reduced in the skeletal muscle in morbid obesity. Downregulation of GLUT4 in adipocytes is considered to be the major factor contributing to the decrease in insulin-stimulated glucose transport in all types of obesity and T2DM. However, GLUT4 expression in the skeletal muscle of obese and diabetic subjects was normal. The defect in glucose transport is suggested to be due to docking, fusion, or impaired translocation of GLUT4-containing vesicles with the plasma membrane. All of the activity of insulin hormone is not proven to be impaired in individuals with obesity and T2DM, although insulin resistance is characteristic of obesity and T2DM (40).

In several epidemiological studies conducted to find the causes of variation in GGT in humans, insulin resistance has been included.

GGT in prospective studies of individual diseases

Studies have been conducted to examine the relationship between GGT and the development of heart disease, hypertension, stroke, and non-insulin-dependent diabetes mellitus (NIDDM).

A cohort study conducted in the United Kingdom examined the relationship between initial GGT values and death from all causes. The study recruited 7600 men through their general practitioners for 11 years or more. Increased GGT has been reported to be significantly associated with increased all-cause mortality (41).

Based on the information about GGT, it was considered as a predictor of the development of NIDDM, which was followed up for 13 years. GGT is considered a marker that indicates fatty liver and abdominal obesity, which thereby suggests the incidence of insulin resistance. A correlation was evident between NIDDM diagnosed throughout the

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time of follow-up and GGT levels measured initially. The GGT measurements obtained at the beginning of the study were found to be significantly higher in men who were later diagnosed with NIDDM. In contrast, the risk of developing NIDDM was reported to be continuously elevated with cumulative GGT (8).

A significant positive association was observed between GGT and smoking, alcohol intake, BMI, triglycerides, and heart rate, whereas physical activity was negatively associated. Furthermore, a significant positive weak association was evident between GGT and high-density lipoprotein cholesterol (HDL) (r= 0.04, *P*= 0.0007) and serum glucose (r= 0.05, *P*< 0.0001). Weak associations have been shown between NIDDM risk and other liver function tests such as aspartate aminotransferase (AST), alkaline phosphatase, and albumin (42). The authors conclusively suggested including GGT in the group of vascular risk factors leading to the formation of insulin resistance syndrome (8).

GGT and non-insulin-dependent diabetes mellitus

The possibility of identifying future cases of diabetes aids in implementing preventive measures that lead to more advanced and improved outcomes.

Several studies have investigated and reported the prevalence of abnormal elevation of GGT among diabetics, but most studies have omitted the investigation of the prevalence in healthy controls.An increased prevalence of raised GGT was confirmed by a study conducted on 411 diabetic outpatients, and some of the patients also had increased levels of aspartate aminotransferase (AST) (42) and alanine aminotransferase (ALT) (20). Glycemic control, a type of diabetes treatment used, or duration of diabetes did not appear to influence the rate of GGT abnormality (43).

A study conducted in Italy reported that abnormal GGT was highly prevalent among diabetic patients. The authors excluded diabetics with abnormal AST or ALT levels and then compared the prevalence in diabetics and controls and found no difference between groups (44).

A study that assessed the effect of the type of diabetes and the relationship between the increases in GGT reported no increase in serum GGT activity in insulin-dependent diabetics of both males and females when compared with the controls. However, the median serum GGT activity was twice as increased in NIDDM patients compared with same-sex controls. Moreover, BMI was significantly and positively correlated with GGT in both controls and diabetics (14).

Studies conducted on GGT and mortality have described associations between the presence of diabetes at the time of entry into the study and the GGT level (41,45). Considerably higher serum GGT was found in a cohort study on diabetes, and diabetes was strongly positively related to serum GGT (45). There was a significant positive association between GGT and DM. The authors summarized that increased levels of GGT are associated with many factors other than alcohol intake, such as DM, BMI, and serum total cholesterol. Strong associations of GGT with all-cause mortality were observed (41).

A study conducted in Japan investigated the relationship between glucose tolerance and GGT in subjects divided into three classes: normal, impaired glucose tolerance (IGT), and DM. They were divided according to the results of the 75-g OGTT. The prevalence of increased serum GGT levels was significantly higher in subjects with IGT (51.0%, *P*< 0.005) and DM (16.2%, *P*< 0.05) than in normal subjects (5.4%). Mean GGTs of both IGT (21.2 ± 10.0 U/L, *P*< 0.001) and DM (19.1 ± 7.1 U/L, *P*< 0.05) were also significantly higher than those of normal subjects (16.4 ± 7.5 U/L). The authors indicated the prevalence of high serum GGT levels as an important concomitant of GGT (46).

Several prospective studies have reported an association between increased risk of T2DM and a graded response of increasing serum

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GGT activity even within the reference interval after adjusting for confounding factors (8,47-49). Obesity showed a strong association with T2DM in women with GGT equal to or greater than the median GGT, but in men, obesity was associated with T2DM even if the GGT levels were below or above the median (48).

GGT enzyme was reported to be a predictor of diabetes and hypertension with increasing levels across the quartiles investigated by the Coronary Artery Risk Development in Young Adults (CARDIA) study (50). In this longitudinal study, the risk of developing microalbuminuria in young white and black men and women with diabetes and hypertension was predicted by GGT activity within the reference range (51). Therefore, the sequential measurement of serum GGT activity was considered a useful predictor of the risk of complications in patients with DM.

The altered function of GGT is believed to be associated with alcohol abuse, obesity, liver disease, risk factors for cardiovascular disease, and enzyme activity, according to the available data. The association is found to be dependent on GGT activity in regulating glutathione levels in the event of depletion. Recently conducted relevant studies underpin these postulations (3). Several available population-based cohort studies have consistently reported an association between increased serum GGT activity and an increased risk of major vascular and non-vascular outcomes, especially cardiovascular disease morbidity and mortality and incident T2DM, even within the normal reference range. These associations have been observed in both men and women in different ethnic groups and among self-reported non-drinkers. A few studies have adjusted these associations for several traditional and non-traditional risk factors, whereas the associations appeared to be independent of established risk factors. People identified with elevated GGT in the spectrum of associated diseases are advised and likely to benefit from dietary changes, weight loss, and increased physical exercise. The best use of serum GGT activity in risk estimation is suggested by adding it to routinely performed measurements to assess pre-diabetes and cardiovascular risk and to make decisions on treatments. However, it requires massive investment for clinical applications in safety and efficacy studies (36).

A strong, positive, graded association was evident between baseline serum GGT activity and the incidence of T2DM, mostly within the normal range, in a study conducted on healthy Korean men. The adjusted relative risks (RR) for incident diabetes among subjects with GGT concentrations of 10-19 U/L, 20-29 U/L, 30-39 U/L, 40-49 U/L, and over 50 U/L were reported 13.3, 12.6, 19.6, and 25.8, respectively, compared with the subjects who had GGT concentrations less than 9 U/L (52).

Several researchers have investigated and confirmed that elevated ALT and GGT activities are associated with T2DM (53-59). Increased serum GGT and ALT activities were found to be independent risk factors for the development of type 2 diabetes in subjects without liver dysfunction or fatty liver after confirmation by ultrasonography (60).

GGT and insulin resistance

In several epidemiological studies conducted to investigate the causes of variation in GGT in humans, an association with insulin resistance has been observed. Insulin resistance has generally been assessed from the plasma insulin concentrations measured during an OGTT or from fasting plasma insulin measurements because it is difficult to test large numbers of subjects using the glucose clamp protocol (3).

In a population study of 4763 middle-aged men, the 2-h responses of blood glucose and plasma immune-reactive insulin (IRI) were studied. The subjects were divided into subgroups with different levels of GGT and/or defined alcohol consumption. A blood glucose level of ≥7.0 mmol/L measured after 2-h has been considered indicative of IGT. Both 2-h blood glucose and plasma IRI were lower than in the whole screening cohort in the group

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with low GGT (below the median, n=2196). The 2-h mean blood glucose increased from 4.9 mmol/l in the men with the lowest GGT to 6.8 mmol/l in the men with the highest GGT group, and both of these values were significantly different ($P< 0.0005$) from the whole cohort. However, in the group with increased screening GGT, both fasting and especially, 2-h blood glucose and plasma IRI were higher than in the average males (61).

Similar results were reported by other studies, and a highly significant elevation was observed in serum insulin with higher GGT levels. This association was found within the reference range fGGT. The mean insulin levels of fasting, 1-h, and 2-h values in the glucose tolerance test were approximately twice increased in subjects with GGT 16-25 U/L at 25 compared to those with GGT of 8 U/L at 25 or less (62,63).

The relationship between GGT activity and the components of metabolic syndrome was analyzed by recruiting male and female hypertensive patients taking medication aged 40-59 years at the time of selection along with age- and sex-matched controls. The effect of GGT activity on different insulin measures was also assayed. Levels of GGT were correlated with BMI and alcohol intake as expected, but correlations with components of the metabolic syndrome persisted after correction for BMI and when only results from non-drinkers were analyzed (64).

Two mechanisms for the association were considered by the authors: first, GGT is increased due to insulin resistance, which is associated with fatty liver, and second, disturbed glucose metabolism may affect GGT more directly. The direct association of insulin resistance with increased GGT provides a potential unifying factor to connect GGT with obesity and fat distribution, hypertension, dyslipidemia, smoking, exercise, and total mortality or cardiovascular and cerebrovascular risk (64).

Potential mechanisms involved in the association between GGT and T2DM

Several mechanisms have been proposed to explain the association between GGT and T2DM. GGT is considered an indicator of oxidative stress, and its activity is increased to maintain intracellular glutathione levels upon depletion. This enzyme is also a marker of visceral fat, hepatic steatosis, and hepatic insulin resistance (65). Serum GGT has its highest activity in organs with transport functions, such as the kidneys, and is also regarded as an index of liver damage (66).

Furthermore, because of normal cell turnover and cellular stress, GGT leaks into the serum. Accordingly, elevated serum GGT activity aids in identifying subjects with persistent elevation in cellular and oxidative stress. The pro-oxidant activity of GGT during the catabolism of extracellular GSH involves the reduction of ferric ions to ferrous ions, which thereby generates reactive oxygen species (superoxide and hydrogen peroxide). This would induce oxidative stress in cells, and finally, subclinical inflammation plays a key role in the pathogenesis of diabetes as a manifestation of oxidative stress.

Accumulation of fat in the liver could stimulate the production of inflammatory cytokines such as tumor necrosis factor-α and interleukin-6, which influence the metabolism of fatty acids in the liver, leading to the formation of fatty liver (67). Impaired insulin secretion and insulin resistance are major pathophysiological characteristics of T2DM. Accordingly, oxidative stress, increased inflammation, and underlying fatty liver involved in impaired insulin secretion and insulin resistance could link elevated GGT levels to the development of T2DM (1).

Serum C-reactive protein (CRP), which is a marker of inflammation, has been demonstrated to have a strong correlation with GGT. It has been suggested that GGT elevation signifies chronic inflammation, which may represent impaired insulin signaling in the liver (1). Elevated serum GGT activity could be seen before the increase in

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serum CRP concentrations (50). A statistically significant positive linear relationship was evident between serum GGT and serum high-sensitivity CRP concentration (hs-CRP) (r= 0.80, *P*< 0.0001) and with glycemic control. Available studies show significantly elevated concentrations of GGT and hs-CRPP in serum of T2DM patients with poor glycemic control compared with healthy individuals and T2DM patients with good glycemic control. The pathogenesis of diabetes and its complications and poor glycemic control appear to be associated with oxidative stress and inflammation. This suggests a link between oxidative stress, inflammation, and glycemic control in the pathogenesis of patients with T2DM (68).

In addition, some studies have evaluated the relationship between total differential white blood cell (WBC) count and the components of insulin resistance syndrome. The associations of WBC count with obesity, dyslipidemia, glucose intolerance, and hypertension are reported to be identical to those of the components of insulin resistance syndrome. Therefore, an elevation in the WBC count has been postulated as an expression of an insulin-resistant state representing the underlying mechanism (69).

Therefore, serum C-reactive protein concentration and white blood cell count will increase in association with elevated GGT, suggesting inflammation (49,70-72).

GGT and obesity

Studies conducted in Norway including 22 000 subjects, males and females aged 12–62 years, reported that in both genders, BMI had the strongest association with GGT than the effects of alcohol use, blood pressure, physical activity, or serum lipids, according to multiple regression analysis (6,73). A similar association between BMI and GGT was reported in teetotalers vs. alcohol consumers and it appeared that BMI had a greater effect on GGT in men than in women, which may be attributed to the different body fat distribution in men and women (6,73).

Similar studies reported significant associations between BMI and GGT in Italy (1991) (13), Japan (1994) (4), the UK (1995) (41), Sardinia (1996) (74), and the USA (1998) (11).

An overall association was found between GGT and BMI in a Finnish study, and a significant interaction between BMI and alcohol intake was also reported. Based on the published data, the probability of an abnormal GGT (50 U/L or greater) was considered to increase more steeply with increasing alcohol intake in subjects with a BMI of 27 kg/m^2 or more than in subjects with a BMI less than 27 kg/m^2. In non-obese subjects, the probability of an increased GGT result was lower in subjects taking moderate amounts of alcohol than in lifelong abstainers. The authors have reported a significant elevation of GGT activity with heavy alcohol intake (≥ 300g/week) among non-obese subjects (odds ratio (OR) =2.81, 95% confidence interval (CI) 1.35–5.85] and very light intake of alcohol (≥ 40g/week) among obese subjects (OR= 2.02, 95% Cl 1.11-3.68) (75).

There was an association between increased BMI and diabetes in subjects with serum GGT activity toward the higher margin of the reference interval; however, no association was reported when serum GGT was toward the lower margin of the reference interval. This cross-sectional study from the third National Health and Nutrition Examination Survey (NHANES) suggests a strong relationship between serum GGT activity and obesity and the risk of developing DM (76). Similar findings were evident from three earlier prospective studies that investigated the activity of GGT in BMI groups (47,50,52).

One way of explaining the underlying cause includes subclinical pathological changes that are attributable to obesity, which might already be present in obese individuals with GGT activity in the higher margin of the reference interval, whereas those with GGT activity in the lower margin might be at the beginning of pathological changes or the earlier stage of pathogenesis (15).

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Conclusions

Available evidence indicates that baseline GGT level is directly associated with an increased risk of T2DM, suggesting that it is a risk marker for type 2 diabetes along with a longitudinal increase in GGT over time. Serum GGT elevation could serve as a risk estimate for diabetes and should therefore be treated as an alert sign to consider changes in lifestyle.

The relationship between serum GGT and obesity was investigated using BMI as a measure of obesity. Evidence proves that there is a strong association between BMI and GGT, and fatty liver and insulin resistance are believed to be the intermediate characteristics connecting BMI and GGT.

The narrative review has both strengths and potential limitations. Therefore, the results should be interpreted in the context of the limitations available. The comprehensive and systematic literature search of GGT and T2DM aided in establishing clear and transparent inclusion criteria that mitigated study selection bias. However, this narrative review has not specified a clear timeframe for study inclusion, resulting in the inclusion of older studies while excluding more recent research. In addition, relying on highly cited studies leading to a skewed representation of the literature collectively contributes to the study selection bias. The lack of a systematic methodology would make it challenging for researchers to assess the validity of the findings and replicate the review process. Nevertheless, this review has been written in a more accessible way, making it easier for a broader audience to understand, including clinicians, researchers, and the public with the expectation of generating hypotheses for future studies while highlighting the key concepts of the function of GGT as a risk estimate of T2DM.

In conclusion, studies that have observed associations of GGT with T2DM support the hypothesis that an increase in GGT over time, even within the normal reference range, is associated with a change in markers of insulin resistance with a higher incidence of T2DM in both sexes independent of baseline GGT. Therefore, serum GGT measurement is deduced as a universally standardized and available test that could serve as a clinical indicator of detecting insulin resistance state and monitoring its fluctuations (77).

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Authors' contributions

All authors have accepted responsibility for the entire content of this manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved and approved the version to be published.

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