OPEN ACCESS Freely available online

ISSN: 2572-5629
Diabetes Case Reports

Commentary

Catalysis of Glutamyl Transferase Concentrations in Diabetic Patients

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DESCRIPTION

The mechanisms linking elevated GGT levels to T2DM are not fully understood, but several hypotheses have been proposed. One possible mechanism is that GGT reflects oxidative stress and inflammation, which are known to impair insulin signaling and glucose metabolism. Another possible mechanism is that GGT mediates the catabolism of glutathione, which may affect the availability of cysteine and glycine, two amino acids that are involved in glucose homeostasis. A third possible mechanism is that GGT is associated with NAFLD (Non-Alcoholic Fatty Liver Disease), which are a common comorbidity of T2DM and a source of hepatic insulin resistance.

Gamma-Glutamyl Transferase (GGT) is an enzyme that catalyzes the transfer of a gamma-glutamyl group from one molecule to another. It is mainly found in the liver, but also in other tissues such as the kidneys, pancreas, and intestines. GGT plays a role in the metabolism of glutathione, a major antioxidant that protects cells from oxidative stress and detoxifies xenobiotics. GGT also participates in the synthesis and degradation of amino acids, peptides, and leukotrienes. However, recent studies have suggested that GGT may also be involved in the pathogenesis and prognosis of metabolic and cardiovascular disorders, such as obesity, insulin resistance, Type 2 Diabetes Mellitus (T2DM), dyslipidemia, hypertension, atherosclerosis, and coronary heart disease. T2DM is a chronic metabolic disorder characterized by hyperglycemia due to impaired insulin secretion and/or action. It is a major risk factor for CVD (Cardiovascular Disease), kidney failure, blindness, amputation, and premature death. Several epidemiological studies have examined the relationship between serum GGT levels and T2DM risk in different populations. A meta-analysis of 20 prospective cohort studies involving 233, 211 participants and 22, 515 incident cases of T2DM found that higher GGT levels were associated with an increased risk of T2DM. The pooled Relative Risk (RR) for the highest *versus* the lowest category of GGT was 1.64 (95% Confidence Interval (CI): 1.46-1.84), with a dose-response relationship of 1.26 (95% CI: 1.19-1.33) per standard deviation increment of log-transformed GGT. The association was c onsistent across subgroups by sex, ethnicity, geographic region, follow-up duration, adjustment for potential confounders, and diagnostic criteria for T2DM.

CVD is a leading cause of morbidity and mortality among patients with T2DM. It accounts for about half of all deaths in this population. Several studies have investigated the association of GGT levels with CVD risk in patients with T2DM. A meta-analysis of seven prospective cohort studies involving 18 809 participants and 3029 CVD events found that higher GGT levels were associated with an increased risk of CVD mortality. The pooled RR for the highest *versus* the lowest category of GGT was 1.51 (95% CI: 1.23-1.86), with a dose-response relationship of 1.14 (95% CI: 1.07-1.21) per standard deviation increment of log-transformed GGT. The association was stronger for ischemic heart disease than for stroke. The mechanisms linking elevated GGT levels to CVD are likely to be similar to those for T2DM, as both conditions share common risk factors and pathophysiological pathways. In addition, GGT may also contribute to endothelial dysfunction, vascular inflammation, plaque instability, thrombosis, and cardiac remodeling by modulating the bioavailability of nitric oxide, hydrogen sulfide, homocysteine, and other vasoactive substances.

Cancer is another major complication of T2DM that increases the risk of mortality. Several studies have explored the association of GGT levels with cancer risk in patients with T2DM. A meta-analysis of six prospective cohort studies involving 19 340 participants and 754 cancer deaths found that higher GGT levels were associated with an increased risk of cancer mortality. The pooled RR for the highest *versus* the lowest category of GGT was 1.43 (95% CI: 1.13-1.81), with a dose-response relationship of 1.09 (95% CI: 1.02-1.16) per standard deviation increment of log-transformed GGT. The association was stronger for liver cancer than for other cancers. The mechanisms linking elevated GGT levels to cancer are complex and multifactorial. One possible mechanism is that GGT reflects chronic inflammation and oxidative stress, which are known to promote carcinogenesis by inducing DNA damage, epigenetic alterations, genetic instability, cellular proliferation, angiogenesis, invasion, metastasis, and immune evasion.

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Received: 02-May-2023, Manuscript No. DCRS-23-21652; **Editor assigned:** 05-May-2023, PreQC No. DCRS-23-21652 (PQ); **Reviewed:** 19-May-2023, QC No DCRS-23-21652; **Revised:** 26-May-2023, Manuscript No. DCRS-23-21652 (R); **Published:** 02-Jun-2023, DOI: 10.35841/2572-5629.23.8.162.

Citation: Grace K (2023) Catalysis of Glutamyl Transferase Concentrations in Diabetic Patients. Diabetes Case Rep. 8:162.

CONCLUSION

In serum, GGT levels are positively associated with T2DM and its complications such as CVD and cancer. These associations may reflect the involvement of GGT in oxidative stress, inflammation, glutathione metabolism, NAFLD, and other metabolic and vascular processes. GGT may serve as a biomarker and a potential therapeutic target for these conditions. However, more studies are needed to confirm the causal role of GGT in these associations and to elucidate the underlying mechanisms and clinical implications. Another possible mechanism is that GGT regulates the metabolism of glutathione and other compounds that may modulate the balance between apoptosis and survival, cell cycle progression, signal transduction pathways, hormone synthesis and action, drug resistance, and tumor microenvironment.