

To Study the Levels of Serum Gamma-Glutamyl Transpeptidase in Individuals Diagnosed with Type II Diabetes Mellitus and its Correlation with Glycated Haemoglobin

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Abstract:

Background: Gamma-glutamyl transpeptidase (GGT), conventionally regarded as a marker of hepatobiliary dysfunction, has emerged as a potential indicator of oxidative stress, hepatic insulin resistance and metabolic dysfunction. This study evaluated serum GGT levels in adults with type 2 diabetes mellitus (T2DM) and examined their relationship with glycated haemoglobin (HbA1c).

Methods: This hospital-based observational cross-sectional study included 90 adults aged >40 years with established T2DM attending the General Medicine outpatient or inpatient services of a tertiary-care hospital in Himachal Pradesh. Demographic, anthropometric and clinical characteristics were recorded. Fasting blood sugar (FBS), HbA1c, GGT, bilirubin, aminotransferases, alkaline phosphatase and serum proteins were measured using standard laboratory methods. Participants were categorised according to HbA1c as 6.5–8.0%, 8.1–10.0% and >10.0%. Associations were evaluated using Spearman's correlation, one-way analysis of variance and Tukey's post-hoc test.

Results: The mean age was 58.19±11.03 years, and 74.5% of participants were overweight or obese. Mean FBS, HbA1c and serum GGT were 182.93±62.30 mg/dL, 8.72±2.96% and 94.28±36.13 U/L, respectively. Serum GGT showed a moderate positive correlation with HbA1c (Spearman's $\rho=0.505$, $p<0.001$), whereas its correlation with FBS was not significant ($p=0.147$, $p=0.165$). Mean GGT increased from 81.32±28.31 U/L in the HbA1c 6.5–8.0% group to 110.76±40.21 U/L in the 8.1–10.0% group and 115.55±36.82 U/L in the >10.0% group ($p<0.001$). GGT was not significantly associated with BMI, diabetes duration or most conventional liver-function parameters.

Conclusion: Serum GGT demonstrated a significant graded association with HbA1c, suggesting that it may reflect chronic glycaemic exposure and associated metabolic or oxidative stress in T2DM. As an inexpensive and routinely available investigation, GGT may complement HbA1c during metabolic assessment; however, it should not be considered a substitute for established glycaemic markers.

Keywords: Gamma-glutamyl Transpeptidase; Glycated Haemoglobin; Type 2 Diabetes Mellitus; Glycaemic Control; Oxidative Stress.

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterised by insulin resistance, progressive beta-cell dysfunction and persistent hyperglycaemia. Its burden is increasing

rapidly: approximately 589 million adults aged 20–79 years are living with diabetes worldwide, a figure projected to reach 853 million by 2050 [1]. In India, the ICMR-INDIAB study estimated the

weighted prevalence of diabetes and prediabetes at 11.4% and 15.3%, respectively, corresponding to approximately 101 million and 136 million individuals [2].

Chronic hyperglycaemia promotes advanced glycation, oxidative stress, endothelial dysfunction and low-grade inflammation, thereby contributing to microvascular and macrovascular complications. Glycated haemoglobin (HbA1c), formed through non-enzymatic glycation of haemoglobin, reflects average glycaemic exposure during the preceding 2–3 months and is central to diagnosis and treatment monitoring [3,4]. However, HbA1c may be misleading when erythrocyte survival or haemoglobin composition is altered, as in anaemia, haemoglobinopathies, recent blood loss, transfusion or chronic kidney disease [3]. This limitation has encouraged investigation of accessible supplementary metabolic biomarkers.

Gamma-glutamyl transpeptidase, more commonly termed gamma-glutamyl transferase (GGT), is a membrane-bound enzyme involved in extracellular glutathione catabolism and cellular antioxidant defence [5,6]. Although routinely interpreted as a marker of hepatobiliary dysfunction and alcohol exposure, higher serum GGT may also indicate hepatic fat accumulation, insulin resistance, oxidative stress and systemic inflammation. Prospective and population-based studies have associated elevated GGT—even within the conventional reference range—with incident T2DM, while obesity may amplify this relationship [7,8]. Among patients with established T2DM, serum GGT has also been reported to rise with poorer glycaemic control and to correlate positively with HbA1c [9]. Nevertheless, observational and genetic evidence does not conclusively establish causality, and GGT is influenced by obesity, alcohol use, fatty liver, drugs and cholestasis [5,10]. Therefore, the present study aimed to determine serum GGT levels in individuals with T2DM and assess their correlation with HbA1c, clarifying its potential value as an adjunct indicator of glycaemic burden.

Materials and Methods

Study Design and Setting: A hospital-based observational cross-sectional study was conducted in the Department of General Medicine in collaboration with the Department of Biochemistry, Maharishi Markandeshwar Medical College and Hospital, Kumarhatti-Solan, Himachal Pradesh. Participants were recruited from the General Medicine outpatient and inpatient services over 18 months following institutional ethics approval. The study evaluated serum gamma-glutamyl transferase (GGT) concentrations and their relationship with glycated haemoglobin (HbA1c) among clinically stable adults with type 2 diabetes mellitus (T2DM).

Sample Size and Sampling: The sample size was calculated using the formula $n = Z^2_{\alpha/2} \sigma^2 / d^2$ at a 5% level of significance, $Z^2_{\alpha/2}$ was 1.96; the anticipated standard deviation of serum GGT was 12.1 U/L, based on a previous study, and absolute precision was approximately 2.5 U/L (20% of the anticipated standard deviation). The minimum calculated sample size was 90. A non-probability consecutive sampling technique was used, and all eligible patients presenting during the study period were approached until the required sample was attained.

Eligibility Criteria: Patients aged over 40 years with T2DM diagnosed according to the 2014 American Diabetes Association criteria—fasting plasma glucose ≥ 126 mg/dL and/or HbA1c $\geq 6.5\%$ (48 mmol/mol)—were eligible. Only clinically stable patients without an acute diabetic complication were enrolled. Patients were excluded if they had known liver disease or hepatic dysfunction, chronic alcohol use, previous splenectomy, rheumatoid arthritis, systemic lupus erythematosus or another active inflammatory disorder, known or suspected malignancy, pregnancy, warfarin therapy, use of hepatotoxic medication, or another major systemic illness likely to alter serum enzyme activity.

Clinical Assessment: Demographic and clinical information was recorded using a structured data-collection form. Variables included age, sex, duration of diabetes and current glucose-lowering treatment, classified as oral hypoglycaemic agents alone, insulin alone, or combined oral therapy and insulin. Height and weight were measured using standard clinical procedures, and body mass index was calculated as weight in kilograms divided by height in metres squared. Participants were classified as having normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), or obesity (≥ 30 kg/m²). Diabetes duration was categorised as <5, 5–10, or >10 years.

Blood Collection and Biochemical Analysis: After an overnight fast of 8–12 hours, 5 mL of venous blood was collected under aseptic precautions and divided between a plain vacutainer and an ethylenediaminetetraacetic acid tube. Serum was separated by centrifugation and maintained at 2–8°C until analysis. Serum GGT was measured by the enzymatic colorimetric method based on the Szasz principle using a Cobas c 311 autoanalyser (Hitachi High-Tech Corporation, Japan). Fasting blood glucose was measured by the glucose oxidase-peroxidase method. HbA1c was estimated in EDTA-anticoagulated whole blood using high-performance liquid chromatography and reported as a percentage. Routine liver-function parameters, including bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total protein, albumin and globulin, were analysed according to validated laboratory procedures.

Participants were stratified by HbA1c into 6.5–8.0%, 8.1–10.0%, and >10.0% categories.

Statistical Analysis: Data were entered in Microsoft Excel and analysed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarised as mean $\pm$ standard deviation and, where appropriate, median and range; categorical variables were reported as frequencies and percentages. Distributional normality was evaluated using the Shapiro–Wilk test. Spearman's rank correlation was designated the primary analysis of the relationship between GGT and HbA1c because HbA1c was non-normally distributed; Pearson's correlation and Kendall's tau-b were additionally calculated as supporting analyses. Mean GGT concentrations across HbA1c, diabetes-duration and treatment groups were compared using one-way analysis of variance after assessing normality and homogeneity of variance with Levene's test. Significant omnibus results were examined using

Tukey's post-hoc test. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Ethical Considerations: The study was approved by the Institutional Ethics Committee of Maharishi Markandeshwar Medical College and Hospital, Solan (letter No. MMMCH/IEC/820, dated 22 April 2024). Participant confidentiality was maintained throughout data collection and analysis.

Results

The mean age of participants was 58.19 ± 11.03 years, with the largest proportion aged 41–50 years (31.1%). Males constituted 56.7% of the cohort. The mean BMI was 29.48 ± 5.09 kg/m²; 28.9% were overweight and 45.6% were obese, giving a combined overweight/obesity prevalence of 74.5%.

The mean duration of diabetes was 7.59 ± 4.10 years, and 41.1% had diabetes for 5–10 years. OHA monotherapy was the most common treatment modality (48.9%), followed by combined OHA and insulin therapy (35.6%) and insulin monotherapy (15.6%) (Table 1).

Table 1: Baseline demographic and clinical characteristics of participants with type 2 diabetes mellitus (N=90)

Characteristic	Category	Frequency (%) / Mean $\pm$ SD
Age (years)	Mean $\pm$ SD	58.19 $\pm$ 11.03
Age group	41–50 years	28 (31.1)
	51–60 years	25 (27.8)
	61–70 years	20 (22.2)
	>70 years	17 (18.9)
Sex	Male	51 (56.7)
	Female	39 (43.3)
BMI (kg/m ²)	Mean $\pm$ SD	29.48 $\pm$ 5.09
BMI category	Normal (18.5–24.9)	23 (25.6)
	Overweight (25.0–29.9)	26 (28.9)
	Obese (≥ 30)	41 (45.6)
Duration of diabetes (years)	Mean $\pm$ SD	7.59 $\pm$ 4.10
Duration category	<5 years	26 (28.9)
	5–10 years	37 (41.1)
	>10 years	27 (30.0)
Treatment	OHA only	44 (48.9)
	Insulin only	14 (15.6)
	OHA + insulin	32 (35.6)

BMI: body mass index; OHA: oral hypoglycaemic agents; SD: standard deviation.

The participants demonstrated suboptimal glycaemic status, with a mean FBS of 182.93 ± 62.30 mg/dL and mean HbA1c of $8.72 \pm 2.96\%$. Serum GGT showed considerable inter-individual variation, with a mean of 94.28 ± 36.13 U/L, median of 91.80 U/L and range of 20.00–180.00 U/L. Mean ALT, AST and ALP levels were 63.71

± 30.61 , 60.56 ± 28.97 and 124.96 ± 38.11 U/L, respectively. Bilirubin and serum protein parameters showed comparatively narrower distributions, with mean albumin and globulin concentrations of 4.18 ± 0.51 and 3.04 ± 0.97 g/dL, respectively (Table 2).

Table 2: Glycaemic and biochemical profile of participants with type 2 diabetes mellitus (N=90)

Parameter	Mean $\pm$ SD	Median (IQR)	Range
Fasting blood sugar (mg/dL)	182.93 $\pm$ 62.30	166.00 (141.25–206.50)	85.00–372.00
HbA1c (%)	8.72 $\pm$ 2.96	7.65 (6.90–8.80)	6.50–18.70
GGT (U/L)	94.28 $\pm$ 36.13	91.80 (71.08–117.55)	20.00–180.00
Total bilirubin (mg/dL)	0.71 $\pm$ 0.23	0.72 (0.56–0.88)	0.30–1.44
Direct bilirubin (mg/dL)	0.23 $\pm$ 0.09	0.24 (0.14–0.28)	0.07–0.41
Indirect bilirubin (mg/dL)	0.48 $\pm$ 0.17	0.46 (0.36–0.60)	0.14–1.04
ALT (U/L)	63.71 $\pm$ 30.61	64.50 (37.00–91.75)	15.00–119.00
AST (U/L)	60.56 $\pm$ 28.97	60.00 (35.25–84.00)	15.00–109.00
ALP (U/L)	124.96 $\pm$ 38.11	123.50 (95.50–155.50)	60.00–196.00
Total protein (g/dL)	7.21 $\pm$ 0.71	7.19 (6.62–7.90)	6.06–8.45
Albumin (g/dL)	4.18 $\pm$ 0.51	4.20 (3.78–4.64)	3.26–4.97
Globulin (g/dL)	3.04 $\pm$ 0.97	3.02 (2.24–3.86)	1.28–4.94

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; FBS: fasting blood sugar; GGT: gamma-glutamyl transferase; HbA1c: glycated haemoglobin; IQR: interquartile range.

Serum GGT demonstrated a statistically significant moderate positive correlation with HbA1c ($\rho=0.505$, $p<0.001$), indicating higher GGT concentrations with increasing long-term glycaemic burden. GGT also showed a weak positive correlation with serum albumin ($\rho=0.238$, $p=0.024$)

and a weak negative correlation with age ($\rho=-0.231$, $p=0.029$). No statistically significant correlations were observed between GGT and BMI, duration of diabetes, FBS, bilirubin fractions, ALT, AST, ALP, total protein or globulin (all $p>0.05$) (Table 3).

Table 3: Correlation of serum gamma-glutamyl transferase with clinical and biochemical variables among participants with type 2 diabetes mellitus (N=90)

Variable	Spearman's ρ	p value	Interpretation
Age	-0.231	0.029	Significant negative
BMI	0.055	0.604	Not significant
Duration of diabetes	-0.020	0.850	Not significant
Fasting blood sugar	0.147	0.165	Not significant
HbA1c	0.505	<0.001	Significant positive
Total bilirubin	0.067	0.532	Not significant
Direct bilirubin	-0.025	0.817	Not significant
Indirect bilirubin	0.076	0.476	Not significant
ALT	0.140	0.188	Not significant
AST	0.000	0.997	Not significant
ALP	-0.017	0.874	Not significant
Total protein	-0.004	0.973	Not significant
Albumin	0.238	0.024	Significant positive
Globulin	-0.142	0.183	Not significant

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; GGT: gamma-glutamyl transferase; HbA1c: glycated haemoglobin; ρ : Spearman's correlation coefficient.

Of the 90 participants, 53 (58.9%) had HbA1c values of 6.5–8.0%, 21 (23.3%) had values of 8.1–10.0%, and 16 (17.8%) had values >10.0%.

Mean GGT increased progressively across these categories from 81.32 ± 28.31 U/L to 110.76 ± 40.21 U/L and 115.55 ± 36.82 U/L, respectively, with a significant overall difference (ANOVA $p<0.001$). Tukey analysis showed significantly

higher GGT in the 8.1–10.0% group than in the 6.5–8.0% group (mean difference 29.45 U/L; 95% CI 9.20–49.69; $p=0.002$).

GGT was also significantly higher in the >10.0% group than in the 6.5–8.0% group (mean difference 34.24 U/L; 95% CI 11.84–56.63; $p=0.001$), whereas the two higher-HbA1c categories did not differ significantly ($p=0.900$) (Table 4).

Table 4: Comparison of serum gamma-glutamyl transferase levels across HbA1c-based glycaemic categories (N=90)

categories (N=56)						
HbA1c category	Frequency (%)	HbA1c, mean $\pm$ SD (%)	GGT, mean $\pm$ SD (U/L)	GGT median (IQR)	GGT range	ANOVA p value
6.5–8.0%	53 (58.9)	7.05 $\pm$ 0.42	81.32 $\pm$ 28.31	83.39 (61.40–99.19)	20.00–151.60	<0.001
8.1–10.0%	21 (23.3)	8.65 $\pm$ 0.51	110.76 $\pm$ 40.21	109.30 (74.19–149.80)	48.48–177.20	
>10.0%	16 (17.8)	14.34 $\pm$ 2.76	115.55 $\pm$ 36.82	117.10 (93.81–141.10)	36.27–180.00	
Tukey post-hoc comparison	Mean difference (U/L)	95% CI	Adjusted p value	Interpretation		
8.1–10.0% vs 6.5–8.0%	29.45	9.20 to 49.69	0.002	Significant		
8.1–10.0% vs >10.0%	-4.79	-30.85 to 21.27	0.900	Not significant		
6.5–8.0% vs >10.0%	-34.24	-56.63 to -11.84	0.001	Significant		

Group means were compared using one-way analysis of variance, followed by Tukey's post-hoc test. CI: confidence interval; GGT: gamma-glutamyl transferase; HbA1c: glycated haemoglobin; IQR: interquartile range.

Mean GGT levels were comparable among participants with diabetes durations of <5 years, 5–10 years and >10 years (93.93 $\pm$ 43.00, 93.73 $\pm$ 35.71 and 95.36 $\pm$ 30.40 U/L, respectively; $p=0.983$), indicating no meaningful association with disease duration. Conversely, GGT differed significantly across treatment modalities ($p=0.041$).

The highest mean GGT was observed among participants receiving insulin alone (115.65 $\pm$ 32.34 U/L), followed by those receiving OHA alone (92.87 $\pm$ 38.44 U/L), while participants receiving combined OHA and insulin therapy had the lowest mean level (86.86 $\pm$ 31.52 U/L) (Table 5).

Table 5: Serum gamma-glutamyl transferase levels according to diabetes duration and treatment modality (N=90)

Subgroup	Frequency (%)	GGT mean $\pm$ SD (U/L)	Median (IQR)	Range	ANOVA p value
Duration of diabetes					
<5 years	26 (28.9)	93.93 $\pm$ 43.00	93.83 (60.30–124.88)	24.00–177.20	0.983
5–10 years	37 (41.1)	93.73 $\pm$ 35.71	92.13 (72.81–115.50)	20.00–163.40	
>10 years	27 (30.0)	95.36 $\pm$ 30.40	90.20 (74.94–115.00)	48.48–180.00	
Treatment modality					
OHA only	44 (48.9)	92.87 $\pm$ 38.44	89.62 (68.52–116.38)	20.00–180.00	0.041
Insulin only	14 (15.6)	115.65 $\pm$ 32.34	116.90 (101.58–126.22)	32.86–164.70	
OHA + insulin	32 (35.6)	86.86 $\pm$ 31.52	84.39 (61.78–99.20)	28.81–163.40	

Group means were compared using one-way analysis of variance. GGT: gamma-glutamyl transferase; IQR: interquartile range; OHA: oral hypoglycaemic agents.

Discussion

The present study demonstrated a meaningful relationship between serum gamma-glutamyl transpeptidase (GGT) and chronic glycaemic exposure in adults with type II diabetes mellitus. Participants had generally inadequate glycaemic control, with mean fasting blood sugar (FBS) of 182.93 $\pm$ 62.30 mg/dL and mean glycated haemoglobin (HbA1c) of 8.72 $\pm$ 2.96%. Mean serum GGT was 94.28 $\pm$ 36.13 U/L, with values ranging from 20 to 180 U/L. The principal finding was a moderate positive correlation between GGT and HbA1c (Spearman's $\rho=0.505$, $p<0.001$), indicating

that higher GGT levels were associated with poorer long-term glycaemic control. The present findings are consistent with prospective epidemiological evidence linking GGT with diabetes and metabolic deterioration. Perry et al. first demonstrated that elevated GGT independently predicted the development of non-insulin-dependent diabetes mellitus [11].

In the KORA study, Meisinger et al., reported progressively increasing diabetes risk across GGT categories, with hazard ratios of 4.24 in men and 2.41 in women when the highest and lowest categories were compared [12]. The Mexico City

Diabetes Study subsequently identified GGT as an independent predictor of progression from normal glucose tolerance to impaired glucose tolerance or diabetes [13]. Similarly, the Hisayama Study found that serum GGT and alanine aminotransferase independently predicted incident diabetes in a Japanese population [14]. Metabolic investigations by Bonnet et al. further demonstrated that liver enzymes were associated with hepatic insulin resistance, compensatory insulin secretion and altered glucagon concentrations [15]. A systematic review of 24 cohort studies involving 177,307 participants and 11,155 incident diabetes cases reported a pooled relative risk of 1.34 for the highest versus lowest GGT thirds and demonstrated a nonlinear dose-response relationship [16].

A distinct graded increase in GGT was observed across HbA1c categories. Mean GGT increased from 81.32 ± 28.31 U/L among participants with HbA1c 6.5–8.0% to 110.76 ± 40.21 U/L in those with HbA1c 8.1–10.0% and 115.55 ± 36.82 U/L in those with HbA1c >10.0% (ANOVA $p < 0.001$). Compared with the 6.5–8.0% category, GGT was significantly higher in both the 8.1–10.0% group (mean difference 29.45 U/L, $p = 0.002$) and the >10.0% group (mean difference 34.24 U/L, $p = 0.001$). Krishnamurthy et al., similarly observed higher GGT levels among patients with poor glycaemic control and reported a positive HbA1c–GGT association ($R^2 = 0.09$, $p = 0.03$) [17]. Sathvika et al., reported an even stronger correlation between GGT and HbA1c ($r = 0.900$, $p < 0.001$) [18]. In contrast, Ren et al., found that GGT was associated with glucose-defined diabetes but not consistently with diabetes defined exclusively through HbA1c, suggesting that diagnostic criteria and population characteristics may influence the association [19]. Balogun et al., also documented frequent GGT and aminotransferase abnormalities among patients with type II diabetes [20]. The lack of a significant difference between the HbA1c 8.1–10.0% and >10.0% groups ($p = 0.900$) may indicate a plateau or nonlinear relationship at severe hyperglycaemia. Moreover, GGT was not significantly correlated with FBS ($p = 0.147$, $p = 0.165$). FBS reflects glucose concentration at a single time point and is influenced by recent diet, medication adherence, stress and acute illness, whereas HbA1c represents cumulative glycaemic exposure over approximately 8–12 weeks. Therefore, GGT may be more closely related to sustained metabolic and oxidative stress than to transient fasting glucose fluctuations. Biologically, GGT participates in extracellular glutathione catabolism and facilitates the recovery of amino acids required for intracellular glutathione synthesis. Persistent hyperglycaemia increases mitochondrial reactive oxygen species generation and glutathione consumption, potentially stimulating GGT expression as a compensatory

response. Consequently, GGT has been proposed as a marker of systemic oxidative stress [21]. GGT-mediated glutathione degradation also produces cysteinyl-glycine, which can participate in metal-dependent redox reactions and further increase oxidative injury [22]. In addition, hepatic lipid accumulation increases free-fatty-acid flux, hepatic insulin resistance and enzyme release. The established association between nonalcoholic fatty liver disease and insulin resistance provides another plausible explanation for higher GGT among patients with poor glycaemic control [23]. GGT was not significantly associated with BMI, diabetes duration, bilirubin, ALT, AST or alkaline phosphatase. The absence of association with BMI may reflect restricted variability because 74.5% of participants were overweight or obese. The similarity of GGT across diabetes-duration categories ($p = 0.983$) suggests that current metabolic control may be more influential than elapsed disease duration. Weak correlations with age ($p = -0.231$, $p = 0.029$) and albumin ($p = 0.238$, $p = 0.024$) should be interpreted cautiously because multiple correlations were examined. Although GGT differed across treatment categories ($p = 0.041$), with the highest level among insulin-only participants, this probably reflects greater disease severity or confounding by indication rather than an adverse effect of insulin. Overall, GGT may serve as a routinely available adjunctive marker of chronic metabolic and oxidative stress; however, the cross-sectional design does not establish causality or justify replacing HbA1c with GGT.

Limitations

This study was limited by its single-centre, cross-sectional design and relatively small sample, which restrict generalisability and precludes determination of temporality or causality. The absence of a non-diabetic control group prevented direct estimation of excess GGT attributable to diabetes. Potential confounders, including hepatic steatosis, dietary factors, physical activity and detailed medication exposure, were not fully assessed. Multiple correlation testing may also have increased the possibility of chance associations.

Conclusion

Serum GGT showed a moderate positive correlation with HbA1c and increased significantly across worsening glycaemic-control categories in adults with type II diabetes mellitus. Its lack of significant association with fasting glucose, diabetes duration, BMI and most conventional liver-function parameters suggests that GGT may reflect cumulative metabolic and oxidative stress more closely than a single fasting glucose measurement. The findings support the potential use of routinely available GGT as an adjunct, rather

than a replacement, for HbA1c in metabolic assessment. Larger multicentre prospective studies incorporating non-diabetic controls, hepatic imaging and comprehensive confounder adjustment are required to establish its independent prognostic and clinical utility.

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