Diabetes, Metabolic Syndrome and Obesity

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Analysis of the Association Between Changes in the GGT/HDL-C Ratio and the Risk of Diabetes Mellitus Based on a Latent Class Growth Mixed Modeling: A Longitudinal Cohort Study of Adults in China

Shichao Liang[1], Tengfei Yang[2]

[1]Department of Emergency Medicine, Shengjing Hospital of China Medical University, Shenyang, People's Republic of China; [2]Department of Health Management, Shengjing Hospital of China Medical University, Shenyang, People's Republic of China

Correspondence: Tengfei Yang, Department of Health Management, Shengjing Hospital of China Medical University, No. 36, Sanhao Street, Heping District, Shenyang, 110004, People's Republic of China, Email yangtf@sj-hospital.org

Objective: Longitudinal cohort analysis was performed to identify the association between changes in the gamma-glutamyl transferase (GGT)/high-density lipoprotein cholesterol (HDL-C) ratio trajectory and the risk of developing diabetes mellitus.

Methods: This was a retrospective cohort study. We analyzed the latent trajectory classes of changes in the GGT/HDL-C ratio by applying a latent class mixture model with healthy individuals who underwent medical checkups from January 2017 to December 2021 as the study subjects. To analyze the effect of the GGT/HDL-C ratio trajectory classes on new-onset diabetes mellitus, we then applied a multivariate Cox proportional risk regression model. Statistical analysis was performed using the R-software with the LCMM package.

Results: The study cohort comprised 3410 participants. All participants were followed up for 5 years, and 95 developed diabetes (4-year incidence of 2.78%). By applying the latent class mixed model, we categorized participants into three trajectory groups: low-stability group (n = 2253), medium-increase group (n = 941), and high-increase group (n = 216). The Cox proportional risk regression model analysis showed that the hazard ratio (95% confidence interval) for the incidence of diabetes mellitus was 1.73 (1.04–2.87) in the medium-increase group and 3.96 (2.11–7.44) in the high-increase group. Moreover, we calculated the estimated model-based levels and linear slopes of the GGT/HDL-C ratios for each age group between 26 and 85 years at 10-year intervals, respectively. The results indicated the strongest correlation between the GGT/HDL-C ratio slope and diabetes in the 46–55 year age group, with an odds ratio of 1.51 (1.25–1.83).

Conclusion: A large increase in the GGT/HDL-C ratio was highly associated with the risk of developing diabetes mellitus. This result suggests that vigilance for changes in the GGT/HDL-C ratio trajectory during community health screening can help identify potential patients with diabetes, enabling early intervention and treatment.

Keywords: GGT/HDL-C ratio, trajectory analysis, diabetes mellitus, cohort study, health management

Introduction

Rapid advances in medical care have increased life expectancy worldwide. However, due to population growth and aging, the burden of noncommunicable chronic diseases (NCDs) has also increased.[1] The four leading NCDs, including diabetes, were the cause of approximately 33.3 million deaths in 2019, representing a 28% increase compared with 2000.[2] When focusing on the individual dimension, the overall risk of dying from chronic respiratory diseases, cardiovascular diseases, and cancers is decreasing globally. In contrast, the risk of dying from diabetes is the only risk that has increased.[3] The International Diabetes Federation World Diabetes Map (10th edition), estimated that 537 million

Received: 22 April 2024
Accepted: 16 August 2024
Published: 24 August 2024

people would develop diabetes in 2021 and that more than 6.7 million people between 20 and 79 years of age would die from diabetes-related causes, translating into an average of one death every 5 seconds.[4] Meanwhile, the number of adolescents and children younger than 19 years old with diabetes is constantly increasing.[5] Hyperglycemia during pregnancy also affects approximately one in six pregnant women.[2] In addition, it was estimated that in 2021, 541 million people with impaired glucose tolerance were at high risk of developing type 2 diabetes (T2DM) and that nearly 45% of individuals with T2DM are undiagnosed.[6] China, with 141 million patients with diabetes, has the highest number of individuals with diabetes in the world.[7] Moreover, the prevalence of diabetes in China is significantly higher than that globally, and it continues to grow rapidly.[8] This fact has led to an urgent need to improve the capacity to diagnose diabetes and to proactively develop a predictive model that provides early, accurate, and timely monitoring for all population groups at risk of developing diabetes. For patients with confirmed diabetes, comprehensive management strategies should be adopted to effectively glycemic control, prevent complications, and improve the quality of life from the three key dimensions of diet, exercise, and medication.

Gamma-glutamyl transferase (GGT) is an inducible enzyme in amino acid metabolism. Serum GGT is mainly derived from the hepatobiliary system.[9] It is widely used in clinical practice as a sensitive but nonspecific indicator of liver function impairment.[10] On the contrary, several prospective studies have identified an association between GGT and insulin resistance, with an elevated GGT level being identified as an independent risk factor for T2DM.[11–13] Research has revealed that high-density lipoprotein cholesterol (HDL-C), can stimulate glucose uptake and improve β-cell function, with a reduced HDL-C level reflecting decreased β-cell function and insulin resistance.[14,15] Furthermore, multiple studies have demonstrated that lower HDL-C levels are associated with an increased risk of diabetes.[16–18] Several studies have provided evidence of the ratio of GGT to HDL-C as a predictor of the prevalence of Metabolic dysfunction-associated steatotic liver disease (MASLD), which showed a significantly higher predictive efficacy than a single indicator.[19–21] To date, little attention has been directed to the role of the GGT/HDL-C ratio in patients with diabetes has received limited attention. Existing studies are predominantly cross-sectional and could not screen and predict high-risk populations.[16,22,23]

A conventional cohort study approach, which focuses on the GGT/HDL-C ratio at baseline and diabetes prevalence status at the end of follow-up would neglect the dynamic changes in the GGT/HDL-C ratio over the lifespan of the study population. In contrast, a longitudinal cohort study collects repeated measurements of the GGT/HDL-C ratio at different times (ages) over the life course, focusing more on the dynamic pattern of variations. According to the theory of life course epidemiology, the GGT/HDL-C ratio has a distinct dynamic pattern of change (growth trajectory) over the life course, with different characteristics of the GGT/HDL-C ratio trajectory showing different effects against diabetes. In our investigation, we found a lack of studies on the relationship between the longitudinal trajectory of the GGT/HDL-C ratio and new-onset diabetes in China and worldwide. To address this gap, we constructed a dynamic physical examination cohort in this study using longitudinal physical examination data collected from 2017 to 2021 at Shengjing Hospital of China Medical University. We analyzed the association between the longitudinal trajectory of the GGT/HDL-C ratio and new-onset diabetes to provide a basis for diabetes prevention and treatment.

Materials and Methods

Study Subjects

We collected physical examination data of individuals attending an annual health checkup from January 2017 to December 2021 at Shengjing Hospital of China Medical University. This study was approved by the Ethics Committee of Shengjing Hospital of China Medical University (IRB reference No. 2021PS190J). We used physical examination data of 2017, the first annual medical checkup data in this study, as the baseline for subject observation. Patients who underwent health checkups in the consecutive years of 2018, 2019, 2020, and 2021 were selected for repeated-measurement monitoring. The contents and methods of health checkups were consistent each year, including epidemiological questionnaires, body measurements, and blood tests for biochemical indicators. After applying the inclusion and exclusion criteria, we included 3410 individuals in this study. Inclusion criteria were (1) subjects had completed 5 consecutive years of health checkups and (2) a complete set of data was available for the subject, including GGT and HDL-C values, from the five health checkups. The exclusion criteria were (1) individuals who refused to

participate in this study, (2) those who were diagnosed with diabetes mellitus on the first physical examination, (3) those missing GGT and HDL-C values during the physical examination, (4) those with cancer, liver disease, cardiovascular disease, or a history of severe rheumatism at baseline screening, and (5) those taking medications affecting the GGT and HDL-C values. Figure 1 presents the details of the inclusion and exclusion process.

Data Collection

Physical examination information was collected at baseline and at each follow-up visit and included the following: (1) Demographic characteristics (age, gender, etc) were collected through face-to-face standardized questionnaire interviews by a designated person. (2) Anthropometric indicators, including height and body weight, were collected by trained doctors and nurses. Height and body weight were measured with the subject wearing light, thin clothing. Height was measured to the nearest cm, and body weight was measured to the nearest kg. (3) For blood biochemical index test, the subject fasted from food and water after 00:00 on the examination day. Venous blood was drawn at 08:00 a.m. to test fasting blood glucose, liver function indices, and lipids. All tests used consistent reagents and methods at the Laboratory Center of Shengjing Hospital, China Medical University. Primary Equipment Name:XN-1000 hematology analyzer (Sysmex Corporation, Kobe, Japan) and automatic biochemical analyzer (OLYMPUS AU 640, Olympus Optical Co., Tokyo, Japan).

Relevant Definitions

We defined diabetes according to the American Diabetes Association criteria (2024 version) as meeting any of the following criteria[24]: (1) self-reported diagnosis of diabetes by a physician during follow-up, (2) use of medications for treating diabetes in the past 2 weeks, (3) fasting blood glucose level ≥7.0 mmol/L (126 mg/dL) along with typical symptoms, (4) glycosylated hemoglobin (HbA1c) ≥ 6.5%, and (5)In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

Statistical Methods

In this study, we explored the potential grouping of individual GGT/HDL-C ratio growth trajectories using a latent class growth mixed modeling (LCGMM). LCGMM partitions heterogeneous populations by estimating latent classes and models individual trajectories using linear mixed models.[25,26] The GGT/HDL-C ratio growth trajectory model was set as

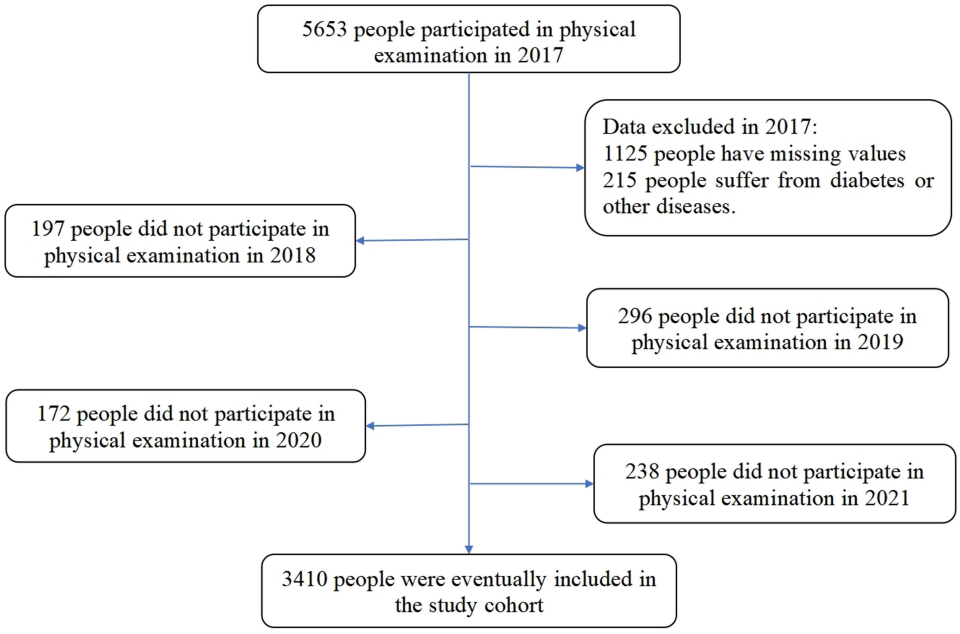

Figure 1 Flow chart showing records that were excluded from the physical examination database.

a polynomial function of age. We fit the LCGMM models traversing polynomial primary to cubic functional forms. Models with trajectories grouped in groups 1–5 were fitted separately in each functional form, and the optimal models were screened according to the following principles: (1) Bayesian information criterion was lowered by at least 20, (2) the average a posteriori probability of each trajectory group was >0.7, and (3) the proportion of individuals with a high a posteriori probability (>0.7) in each group was >0.65. To avoid the LCGMM model converging to a local optimality, we set random starting parameters for the model with a group number 1 and performed multiple fits for each model separately.

SPSS 22.0 and R-language software (version 4.2.1) were applied for statistical analysis. Because the measurement data were not normally distributed, measurements were represented as medians and quartiles, and the two independent-samples Mann–Whitney *U*-test was used to compare the data between the two groups. Count data were expressed as relative numbers, and intergroup comparisons were performed using the χ^2 test. We used the Cox proportional risk model to analyze the hazard ratios (HRs) and 95% confidence intervals (95% CIs) of different GGT/HDL-C ratio trajectories against diabetes mellitus, with a p <0.05 (two-sided test) being considered as a statistically significant difference.

We fitted the growth function of the GGT/HDL-C ratio with age using both fixed-effects and random-effects coefficients estimated by the LCGMM model. The model provided estimates of the GGT/HDL-C ratio and the slopes of GGT/HDL-C ratio growth for individuals grouped by 10-year age intervals over the age range of 26–85 years. We then calculated the correlations between these estimates and diabetes outcomes for each individuals. A logistic regression model was used to determine the standardized odds ratios (ORs) and their 95% CIs.

Sensitivity analysis: We conducted a sensitivity analysis to verify the robustness of the results. To reduce the randomness of diabetes incidence during short-term follow-up, the GGT/HDL-C ratio of each trajectory group was removed from the incidence population in the first year of follow-up after which the LCGMM model was rebuilt. Finally, multivariate Cox regression analysis was conducted on the aforementioned populations, and the results were compared with the main results of this study to evaluate their robustness.

Results

Overview of Baseline Data

We included 3410 adults in the analysis, with 1192 (34.95%) males and 2218 (65.04%) females, who were followed up for 5 years. The median age at baseline examination was 41 (35, 55) years. Table 1 summarizes the baseline characteristics of the variables included in this study based on the incidence of diabetes during the follow-up period. Among the subjects with diabetes mellitus, a higher proportion were males and older These individuals also has elevated levels of GGT/HDL-C ratio, triglyceride, HDL-C, apolipoprotein A-I (apoA-I), apolipoprotein B (apoB), white blood cells, aspartate aminotransferase, and Alanine aminotransferase.

Table 1 Baseline Characteristics of the Two Groups According to Incidence of Diabetes Mellitus at Follow-Up

Variables	NG (N=3315)	DM (N=95)	P
Age	40(35–53)	63(48–70)	P<0.01
Gender			0.02
Male	1148	44	
Female	2167	51	
Total cholesterol	4.89(4.31–5.51)	5.03(4.39–5.64)	0.104
Triglyceride	1.01(0.68–1.52)	1.72(1.19–2.68)	P<0.01
High density lipoprotein-cholesterol (mmol/L)	1.4(1.17–1.66)	1.25(1.04–1.46)	P<0.01
Low density lipoprotein-cholesterol (mmol/L)	2.97(2.46–3.52)	3.2(2.56–3.71)	0.117
Apolipoprotein A-I	1.59(1.41–1.78)	1.49(1.34–1.7)	P<0.01
Apolipoprotein B	0.81(0.68–0.98)	0.95(0.79–1.12)	P<0.01
Total protein (g/L)	75(72.1–78.3)	73.9(71.6–77.3)	P<0.01
Albumin (g/L)	46.7(44.7–49.1)	45.5(43.5–47.4)	P<0.01

(*Continued*)

Table 1 (Continued).

Variables	NG (N=3315)	DM (N=95)	P
Albumin to globulin ratio	1.66(1.47–1.88)	1.58(1.44–1.78)	P<0.01
Aspartate aminotransferase (U/L)	21(17–25)	26(20–34)	P<0.01
Alanine aminotransferase (U/L)	23(18–31)	28(18–43)	P<0.01
Gamma-Glutamyl transferase (U/L)	18(13–28)	28(21–47)	P<0.01
Alkaline phosphatase (U/L)	72.1(59.3–88.3)	81.3(72.2–100.8)	P<0.01
Prealbumin (g/L)	0.29(0.25–0.33)	0.29(0.26–0.34)	0.41
Cholinesterase (U/L)	9060(7813–10,486)	10,056(8992–11764)	P<0.01
Total bilirubin (μmol/L)	11.5(8.9–15.1)	11.6(9.6–15.1)	0.53
Direct bilirubin (μmol/L)	3.6(2.7–4.9)	3.3(2.7–4.7)	0.625
Indirect bilirubin (μmol/L)	7.9(5.9–10.2)	8.2(6.7–10.3)	0.304
Total bile acid (μmol/L)	2.34(1.47–3.72)	2.88(1.78–4.19)	0.011
White blood cell count 10^9/L	6.3(5.3–7.3)	6.8(5.7–8.4)	P<0.01
GGT/HDL-C	13.12(8.51–21.87)	23.72(15.87–40)	P<0.01

Abbreviations: NG, normal groups; DM, diabetes mellitus.

We tested 15 models using linear, quadratic, and cubic functions with trajectories grouped into 1–5 groups. Models with more than one group were fit multiple times with random starting parameters based on the model's parameters in the same function form with a group number of one. Based on LCGMM parameters, we chose a 3-class linear model as the best fit (Table 2). The values and slopes of the GGT/HDL-C ratio were estimated based on the incidence of diabetes in patients aged 26–85 years at follow-up.

We identified three different trajectory patterns based on changes in the GGT/HDL-C ratio during the 4-year follow-up (Figure 2): trajectory 1 (low, stable group) accounted for 66.07% of the cases, trajectory 2 (medium-increase group) accounted for 27.6% of the cases, and trajectory 3 (high-increase group) accounted for 6.33% of the cases. All subjects were grouped at baseline examination based on different GGT/HDL-C ratio trajectory groups. As shown in Table 3, the differences in age, gender, triglyceride level, and HDL level were statistically significant ($P < 0.05$) between all groups.

Table 2 Model Fitting Parameters of the LCGMM for GGT / HDL-C in Subjects

No. Latent Class	Polynomial Degree	Loglik	npm	BIC	% Participants Per Class	Mean Posterior Probabilities	% Posterior Probabilities>70%
1	Linear	−65726.23	6	131,501.3	100	NA	NA
	Quadratic	−65699.93	7	131,456.8	100	NA	NA
	Cubic	−65712.38	8	131,489.8	100	NA	NA
2	Linear	−64270.12	10	127,409.4	87.92/12.08	0.9790/0.9341	98.53/91.50
	Quadratic	−64233.52	12	127,332.6	90.21/9.79	0.9854/0.9381	98.90/90.42
	Cubic	−64069.92	14	128,253.7	80.59/19.41	0.9377/0.9349	96.87/92.15
3	**Linear**	**−63544.6**	**14**	**126,051.5**	**66.07/27.6/6.33**	**0.9020/0.8973/0.9404**	**93.83/87.67/93.98**
	Quadratic	−64610.98	17	126,001.1	63.3/29.46/7.24	0.8804/0.8450/0.9294	91.85/82.79/89.88
	Cubic	−63705.36	20	127,573.4	27.6/64.9/7.51	0.8652/0.8968/0.9215	85.33/92.82/88.67
4	Linear	−63388.88	18	125,790.0	63.11/22.7/9.79/4.4	0.9219/0.7901/0.8445/0.9343	92.70/75.97/79.94/92.00
	Quadratic	−62790.16	22	125,759.3	62.91/23.51/4.16/9.41	0.9136/0.7996/0.9398/0.8450	91.94/75.94/93.66/79.13
	Cubic	−63219.32	26	126,650.1	26.86/67.6/3.31/2.23	0.8966/0.8965/0.8874/0.9161	87.88/94.71/81.42/86.84
5	Linear	−62805.27	22	125,789.5	14.13/22.26/49.65/9.24/4.72	0.5617/0.7690/0.7028/0.8256/0.9178	10.58/71.81/45.19/78.73/88.82
	Quadratic	−63,683.15	27	127,585.9	6.95/57.83/18.06/10.41/6.74	0.4670/0.7841/0.6801/0.7162/0.9217	0/75.46/48.86/62.25/88.70
	Cubic	−63109.86	32	126,480.0	1.35/26.16/64.02/6.42/2.05	0.8909/0.8324/0.9015/0.8881/0.9140	82.61/80.61/91.98/83.56/85.71

Notes: The best fitting model is highlighted in bold characters. After analysis by different classes and initial values, linear 3 class model was chosen as the best fitted. No. Latent class: latent class number of the model; Log-Lik: the maximum Log-Likelihood; BIC: the Bayesian information Criterion; % participants per class: proportion of participants per class.
Abbreviation: NA: not applicable.

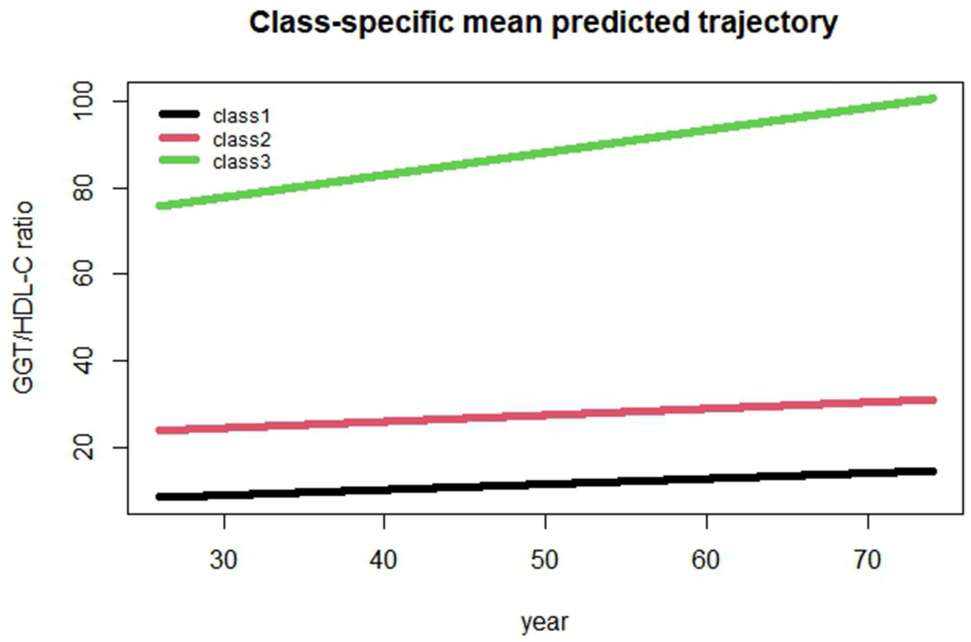

Figure 2 Three different trajectory patterns based on changes in the GGT/HDL-C ratio over time throughout the 4-year follow-up period.

Three Different Grouping Methods and the Distribution of Diabetes Incidence

After we divided the subjects into three groups according to different GGT/HDL-C ratio trajectories, the prevalence of diabetes mellitus was 1.64%, 3.82%, and 10.18%, respectively. When we grouped subjects by considering tertiles of their

Table 3 Baseline Characteristics According to GGT/HDL-C Ratio Trajectory

Variables	Total (N=3410)	Trajectory 1 (N=2253)	Trajectory 2 (N=941)	Trajectory 3 (N=216)	P
Age	41(35–55)	41(35–56)	42(35–53)	40.5(34.25–49)	0.19
Gender					P<0.01
male	1192	409	611	172	
female	2218	1844	330	44	
Total cholesterol	4.89(4.31–5.52)	4.84(4.26–5.46)	4.95(4.4–5.58)	5.2(4.6–5.8)	P<0.01
Triglyceride	1.02(0.68–1.56)	0.86(0.61–1.24)	1.38(0.99–2.02)	1.91(1.28–2.75)	P<0.01
High density lipoprotein-cholesterol (mmol/L)	1.4(1.17–1.66)	1.5(1.3–1.75)	1.19(1.03–1.39)	1.16(0.98–1.39)	P<0.01
Low density lipoprotein-cholesterol (mmol/L)	2.97(2.46–3.52)	2.87(2.38–3.41)	3.14(2.62–3.69)	3.22(2.78–3.83)	P<0.01
Apolipoprotein A-I	1.59(1.41–1.78)	1.65(1.49–1.84)	1.45(1.32–1.62)	1.46(1.29–1.63)	P<0.01
Apolipoprotein B	0.82(0.68–0.98)	0.77(0.65–0.92)	0.9(0.75–1.05)	0.98(0.82–1.14)	P<0.01
Total protein (g/L)	75(72–78.2)	74.7(71.8–77.9)	75.8(72.6–78.7)	76.25(72.8–79.2)	P<0.01
Albumin (g/L)	46.7(44.6–49)	46.4(44.3–48.6)	47.3(45.2–49.7)	47.95(45.7–50.28)	P<0.01
Albumin to globulin ratio	1.66(1.47–1.88)	1.64(1.46–1.86)	1.68(1.49–1.9)	1.73(1.52–1.96)	P<0.01
Aspartate aminotransferase (U/L)	21(17–25)	20(17–24)	22(18–27)	27(22–35)	P<0.01
Alanine aminotransferase (U/L)	24(18–31)	22(17–27)	28(22–39)	40.5(28.25–66.75)	P<0.01
(U/L)	18(13–28)	15(12–19)	30(23–39)	68(51–105.75)	P<0.01
Alkaline phosphatase (U/L)	72.6(59.4–88.5)	69.1(56–85.18)	77.6(65.98–91.4)	84.75(68.63–103.43)	P<0.01
Prealbumin (g/L)	0.29(0.25–0.33)	0.27(0.24–0.31)	0.32(0.28–0.36)	0.35(0.31–0.38)	P<0.01
Cholinesterase (U/L)	9092.5(7836.5–10,528)	8590(7465–9798)	10,021(8874.5–11,370)	10,847.5(9329.25–12,123.25)	P<0.01
Total bilirubin (μmol/L)	11.5(8.9–15.1)	11.2(8.7–14.6)	12.1(9.2–15.6)	12.05(9.1–16.18)	P<0.01
Direct bilirubin (μmol/L)	3.6(2.7–4.9)	3.5(2.6–4.8)	3.8(2.8–5.1)	3.6(2.7–5)	P<0.01
Indirect bilirubin (μmol/L)	7.9(6–10.2)	7.7(5.9–10)	8.3(6.3–10.7)	8.65(6.2–11.08)	P<0.01
Total bile acid (μmol/L)	2.36(1.48–3.75)	2.14(1.36–3.43)	2.74(1.79–4.3)	2.91(1.78–5.42)	P<0.01
White blood cell count (10^9/L)	6.3(5.3–7.4)	6.1(5.2–7.1)	6.6(5.7–7.8)	6.7(6–8.18)	P<0.01

baseline GGT/HDL-C ratios, the incidence of diabetes in each group was 2.46%, 2.55%, and 3.34%, respectively. The differences in the diabetes incidence between groups were statistically significant by the Log rank test (log-rank chi-square = 59.43, 65.91, $P < 0.01$).

Analysis of the Impact of the GGT/HDL-C Ratio Trajectory on the Risk of Developing Diabetes Mellitus by Cox Proportional Modeling

Table 2 details the associations between the different GGT/HDL-C ratio trajectories and the risk of developing diabetes. Model I was a one-way Cox proportional risk model; model II further corrected for baseline triglyceride and apoA-I levels based on model I, and model III further corrected for total protein level, albumin-to-globulin ratio, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and cholinesterase levels as well as white blood cell counts based on model II. In model III, the HR (95% CI) for developing diabetes was 1.73 (1.04–2.87) in trajectory 2 and 3.96 (2.11–7.44) in trajectory 3. These two trajectories showed a higher risk of developing diabetes than trajectory 1 (Table 4).

Baseline GGT/HDL-C ratios were grouped into tertiles. In model III, the HR (95% CI) for developing diabetes in the Q3 tertile group was 5.11 (2.29–11.38), which was statistically different from the Q1 group. In contrast, there was no significant difference between the Q2 and Q1 groups.

Finally, we estimated the ORs of the slope values against the incidence of diabetes mellitus using the GGT/HDL-C ratio model by grouping the data from subjects aged between 26 and 85 years at 10-year intervals. As shown in Figure 3, there was a significant correlation between the GGT/HDL-C ratio estimated by the model and the incidence of diabetes mellitus for subjects aged 26–85 years, except for the 66- to 75-year segment. The estimated ORs of the GGT/HDL-C ratio had a V-shaped distribution. The correlation between the slope of the GGT/HDL-C ratios estimated by the model and the incidence of diabetes mellitus was significantly different only in the age range of 46 −55 years, with an OR of 1.51 (1.25–1.83) (Figure 4).

Sensitivity Analysis

During sensitivity analysis, the GGT/HDL-C ratio from trajectory 1 to trajectories 3, 8, 7, and 5 were excluded due to the incidence of diabetes in the first year of follow-up and because the incidence risk of diabetes in trajectory 3 was 3.64 times that in trajectory 1 (HR = 3.64, 95% CI 1.75–7.58, p = 0.00; Table 5), which was similar to the main results. This finding indicated that the model was stable.

Discussion

This study was the first to demonstrate that a higher GGT/HDL-C ratio trajectory is associated with a greater risk of developing diabetes by analyzing data from 3410 individuals with consecutive 5-year longitudinal GGT/HDL-C ratio

Table 4 COX Proportional Hazards Model of GGT / HDL-C Trajectory and Baseline GGT / HDL-C and Diabetes Mellitus Onset

	New-Cases/ Total(n)	Incidence Density (%)	Model1	Model2	Model3
GGT / HDL-C Trajectory					
Trajectory 1	37/2253	1.64	1	1	1
Trajectory 2	36/941	3.82	2.34(1.48–3.71)	1.97(1.21–3.19)	1.73(1.04–2.87)
Trajectory 3	22/216	10.18	6.4(3.78–10.85)	4.76(2.7–8.38)	3.96(2.11–7.44)
Baseline GGT / HDL-C (quartile)					
Q1 (<9.86)	28/1136	2.46	1	1	1
Q2 (9.86–18.49)	29/1137	2.55	2.01(0.9–4.47)*	1.96(0.87–4.42)*	1.74(0.75–4.04)*
Q3 (>18.49)	38/1137	3.34	7.7(3.84–15.43)	6.76(3.23–14.12)	5.11(2.29–11.38)

Notes: Model 1: Unadjusted. Model 2: adjusted for triglyceride, apolipoprotein A-I. Model 3: adjusted for model 2 plus Total protein, Albumin to globulin ratio, Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Cholinesterase, White blood cell count. * P>0.05; Baseline GGT/HDL-C(quartile):Quartile grouping of GGT / HDL-C ratio at the first physical examination.
Abbreviation: Q = quartile.

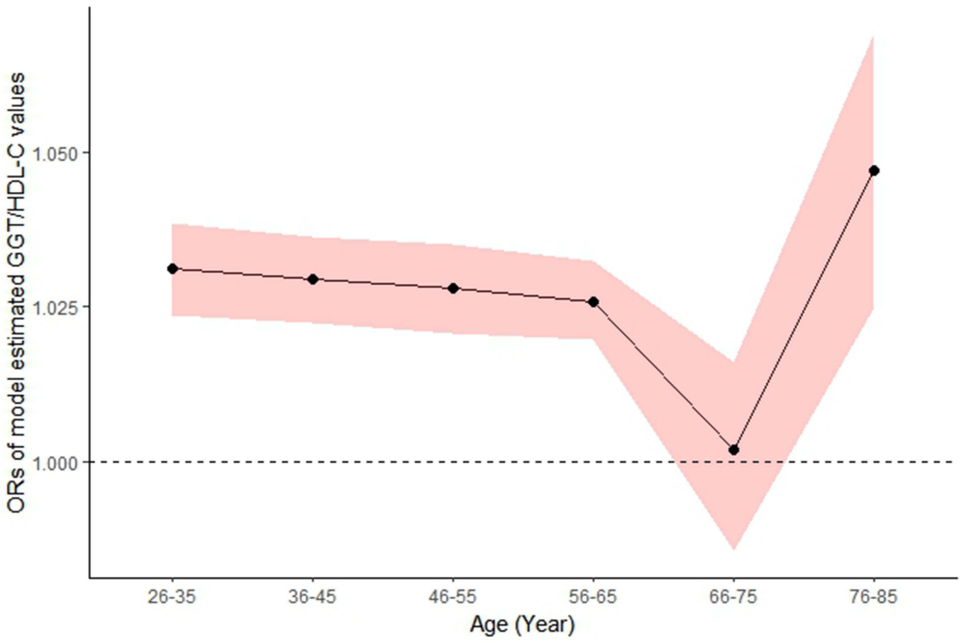

Figure 3 Standardized odds ratios and 95% CIs for the incidence of diabetes mellitus using the model-estimated GGT/HDL-C ratios.

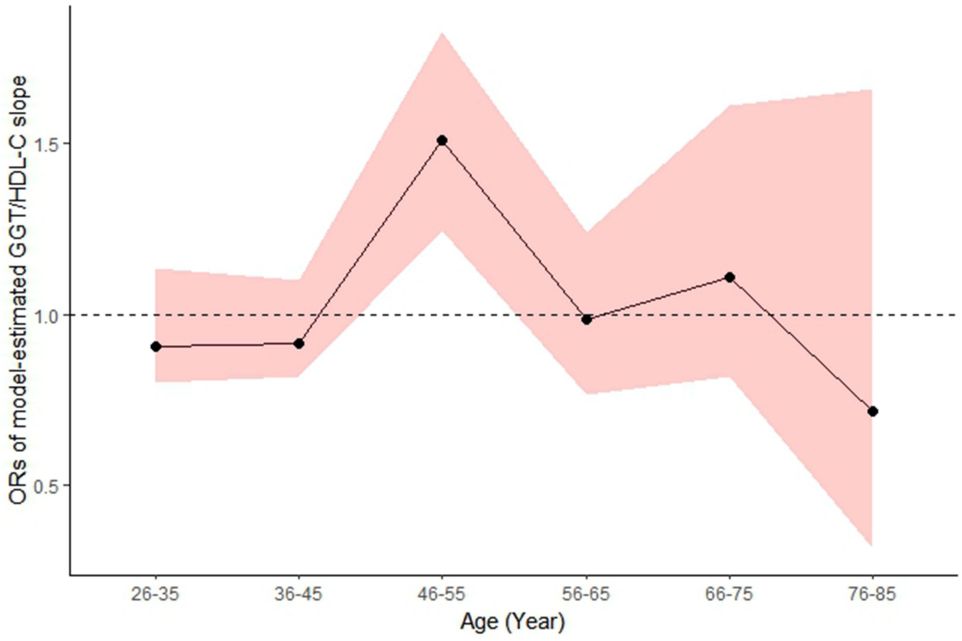

Figure 4 Standardized odds ratios and 95% CIs for the incidence of diabetes mellitus using the model-estimated GGT/HDL-C ratio slope.

measurements. In this study, we calculated the GGT/HDL-C ratio and the slopes of the GGT/HDL-C ratio over 10-year intervals, as estimated by modeling. To investigate the association between these parameters and diabetes mellitus, we fit a logistic regression model. The results revealed that the slope of the GGT/HDL-C ratio in the age range of 45–55 years is potentially significant in predicting the onset of diabetes mellitus.

A conventional cohort study enrolling 15,453 Japanese subjects with a follow-up period of 5.39 years showed that the upper GGT/HDL-C ratio quartile was associated with a significantly higher risk of developing T2DM than the lowest

Table 5 Sensitivity Analysis of Diabetes Incidence Risk in Different GGT / HDL-C Trajectory

	Target Population		Sensitivity Analysis	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value
GGT / HDL-C Trajectory				
Trajectory 1	1		1	
Trajectory 2	1.73(1.04–2.87)	0.03	1.64(0.92–2.92)	0.09
Trajectory 3	3.96(2.11–7.44)	0.00	3.64(1.75–7.58)	0.00

Notes: Adjusted for triglyceride, apolipoprotein A-I, Total protein, Albumin to globulin ratio, Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Cholinesterase, White blood cell count.
Abbreviations: HR, hazard ratios; 95% CI, 95% confidence interval.

GGT/HDL-C ratio quartile (adjusted HR: 1.97; 95% CI: 1.13–3.44). In this study, we divided the GGT/HDL-C ratios in the age range of 25–85 years into three trajectories after trajectory analysis. Among the trajectories, the risk of developing diabetes was 3.96 and 1.73 times higher for subjects in the high- and medium-increase groups than in the stable group, respectively. In addition, the risk of developing diabetes was 3.96 and 1.73 times higher for subjects in the high- and medium-increase groups, respectively, than in the stable group, which is consistent with the trends shown in the previous study's results. However, the LCGMM analysis used in this study differed from the previous cross-sectional and longitudinal approaches. To our knowledge, ours is the first study to address the relationship between the trajectory of the GGT/HDL-C ratio and the incidence of diabetes mellitus. The LCMM package can be used to group population trajectories by estimating potential categories, estimate fixed effects for each trajectory group, fit growth curves for each trajectory group, and further fit growth curves for individuals by estimating individual random effects in addition to fixed effects. Because the LCGMM considers the heterogeneity between trajectory groups and the differences in random effects of individuals within the same trajectory group, it can fit individual growth curves more accurately when performing trajectory analyses. Conventional research methods assume that subjects' GGT/HDL-C ratio trends follow the same pattern and ignore individual developments. Therefore, conventional studies may not adequately reflect the correlation between the GGT/HDL-C ratio and diabetes incidence. By mechanically grouping baseline GGT/HDL-C ratios by tertiles, we also followed the conventional cohort study methodology. The results showed that only the Q3 tertile group had a statistically significant difference in the HR value for developing diabetes (95% CI: 5.11 [2.29–11.38]) compared with the Q1 tertile group, whereas the Q2 tertile group was not statistically different from Q1.

To explore the sensitive period of the GGT/HDL-C ratio growth leading to the onset of diabetes mellitus, we analyzed the trajectory parameters of individual GGT/HDL-C ratio increase in the present study. Subjects who underwent physical examination were categorized into age segments in 10-year intervals. Analysis of the model-estimated GGT/HDL-C ratios yielded fluctuating ORs for diabetes incidence, ranging from 1.019 to 1.069. Except for the intermediate 66–75-year-old segment, we found a correlation between the model-estimated GGT/HDL-C ratio and diabetes incidence for all other age groups from 26 to 85 years. The model-estimated slopes of the GGT/HDL-C ratios were associated with greater ORs for the occurrence of diabetes, which were significantly different only in the 46–55-year age range, with an OR of 1.51 (1.25–1.83). This result suggests a significantly higher risk of developing diabetes in people aged between 46 and 55 years, and thus, extra caution is required when treating patients in this age group.

The liver is a vital organ for glucose metabolism, as it stores and produces glucose as needed by the body, with these processes being primarily regulated by insulin and glucagon. GGT is primarily an active enzyme for extracellular catabolism and metabolism. GGTs are distributed in several body organs and are most abundant in the kidneys, followed by the pancreas and liver. In serum, GGTs mainly originate from the hepatobiliary system. As a sensitive but nonspecific indicator of liver function, the GGT test is widely used in clinical practice in China. Some studies have shown that the presence of diabetes increases GGT activity in the liver rather than in the kidneys[27] A prospective 15-year follow-up study of 4812 subjects identified baseline serum GGT as an independent risk factor for T2DM.[28] *However, the exact mechanism for this has yet to be clearly elucidated. Researchers have contemplated that this manifestation is associated*

with oxidative stress, increased inflammation, and potential fatty liver. GGT plays an important role in the antioxidant system. Its primary function is to maintain intracellular levels of glutathione, whereas reduced glutathione levels contributes to the body's antioxidant capacity. Oxidative stress contributes to insulin resistance[29] and increased oxidative stress precedes the onset of high-fat diet-induced insulin resistance and obesity.[30] T2DM is associated with abnormal inflammatory responses, with typical chronic inflammation occurring in metabolism-related sites such as the liver, muscle, and adipose tissue. Researchers have also observed increased levels of tumor necrosis factor–α in T2DM, whereas interference with inflammatory pathways improved or alleviated insulin resistance. Additionally, a decrease in liver fat content improved insulin's suppression of glucose production, leading to the normalization of fasting blood glucose levels.[31] Therefore, GGT may be a marker for hepatic insulin resistance and steatosis. Kuchay et al,[32] indicated that hyperglycemia in patients with T2DM would lead to the increased production of reactive oxygen species in the mitochondria during metabolism. Reactive oxygen species, as a signaling molecule, can activate multiple stress pathways in cells, thereby causing damage to the IR and islet β-cells. GGT, which belongs to the redox enzymes, is an important component of intracellular antioxidants,[33] and is increased in hyperglycemic conditions.

More than three-quarters of patients with T2DM have metabolic abnormalities, primarily mixed dyslipidemia, including low HDL-C levels. Abnormalities in lipid metabolism are strongly correlated with insulin resistance, visceral obesity, and MASLD.[34] In a double-blind crossover clinical trial in 2009, investigators used a reconstituted HDL, which is a synthetic HDL intravenous injection, to increase HDL levels in 13 subjects with T2DM.[35] The results showed increased insulin secretion and significantly decreased blood glucose levels in the subjects following the elevation of HDL levels. Researchers from South Korea conducted a large cohort study with a sample size of five million people. They showed that excessive fluctuations in HDL-C increased the relative risk of diabetes by up to 40%.[18] HDL-C activates the signaling pathway of adenosine monophosphate-activated protein kinase present in fat, skeletal muscle, and cardiomyocytes, thereby promoting glucose uptake in various peripheral tissues. Hence, a decrease in HDL-C increases insulin resistance and the risk of diabetes rises.[36] The apoA-I and apoA-II are known as the two predominant apolipoproteins in HDLs. Studies have indicated that apoA-I improves the function of pancreatic cells and increases insulin sensitivity in humans. The increase in insulin secretion from β-cells mediated by apoA-I occurs via the G protein–cyclic adenosine monophosphate-protein kinase A (cAMP-PKA)–FoxO1 signaling pathway.[37,38] In addition, apoA-I also increases the expression of the β-cell survival-related gene, Pdx1, resulting in an increased expression of insulin genes and an increased production of insulin.[38]

The GGT/HDL-C ratio is a relatively new indicator, mostly used in studies targeting MASLD and metabolic syndrome.[20] The predictive efficacy of the GGT/HDL-C ratio was found to be significantly higher than that of either GGT or HDL-C alone. A few studies have since used this metric in T2DM populations, but all have been cross-sectional studies.[16,22,23] There is evidence that the association of the GGT/HDL-C ratio with T2DM is significant even when GGT levels are in the normal range, making the definition of predictive thresholds important and difficult. This highlights the significance of dynamic trajectory analysis. The reference value for HDL-C varies based on the patient's risk factors. Therefore, the ratio between GGT and HDL-C may better identify individuals at increased risk for developing diabetes mellitus.

However, there are some limitations to this study. First, the lack of data on the diagnosis of diabetes mellitus through oral glucose tolerance tests may lead to an underestimation of diabetes incidents. Second, to avoid data bias, samples with missing values were deleted. This resulted in less data on diabetes incidence, and further follow-up studies are required. Finally, the model-estimated values of GGT/HDL-C ratios and the ORs for the slope analysis of diabetes incidence were not statistically significant in some age groups, probably because of the small number of participants in that age group.

Conclusion

In general, the findings of this study provide additional insights toward understanding the prevention of diabetes; that is, the steeper the slope of the GGT/HDL-C ratio and the higher the GGT/HDL-C ratio, the higher the risk of developing diabetes. In clinical practice, measurement of GGT and HDL-C using the same blood sample has long been widely applied. Measurements using automated analyzers are fast, inexpensive, accurate, and easy to use for monitoring on

a large scale. Therefore, extra attention should be paid to this group during community health screening, and health interventions within the community should be implemented to prevent diabetes.

Data Sharing Statement

The datasets used and analyzed in the present study could be available from the corresponding author upon a reasonable request.

Ethics Approval and Consent to Participate

This human study was approved by Shengjing Hospital of China Medical University Ethics Committee (ref. Ethics 2021PS190J). It was a retrospective study, without direct intervention. All patient data are anonymous. Subjects' information and privacy are fully protected. Therefore, the institutional review board waived the need for written informed consent provided by participants. This study complied with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

All authors declare that they have no conflicts of interest in this work.

References

1. Dominguez LJ, Di Bella G, Veronese N, et al. Impact of Mediterranean Diet on Chronic Non-Communicable Diseases and Longevity. *Nutrients*. 2021;13(6):2028. doi:10.3390/nu13062028
2. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabet Res Clin Pract*. 2022;183:109119. doi:10.1016/j.diabres.2021.109119
3. World health statistics 2023: monitoring health for the SDGs, Sustainable Development Goals. Available from: http://www.indiaenvironmentportal.org.in/files/file/World%20health%20statistics%202023.pdf. Accessed August 20, 2024
4. Magliano DJ, Boyko EJ. *IDF Diabetes Atlas*. 10th ed. Brussels: scientific committee; 2021.
5. Jean M, Lawrence JD, Isom S. Trends in Prevalence of Type 1 and Type 2 Diabetes in Children and Adolescents in the US, 2001–2017. *JAMA*. 2021;326:1331.
6. The IDF Diabetes Atlas. 10th edition. Available from: https://diabetesatlas.org/atlas/tenth-edition/. Accessed August 20, 2024
7. Shen Y, Wang S, Shen Y, et al. Evaluating the Usability of mHealth Apps: an Evaluation Model Based on Task Analysis Methods and Eye Movement Data. *Healthcare*. 2024;12(13):1310. doi:10.3390/healthcare12131310
8. White Paper on China's Blood Glucose Health Management Industry. 2023. Available from: https://www.xdyanbao.com/doc/djnr4hpxcj?bd_vid=10268943029908311748. Accessed August 20, 2024
9. Mitrić A, Castellano I. Targeting gamma-glutamyl transpeptidase: a pleiotropic enzyme involved in glutathione metabolism and in the control of redox homeostasis. *Free Radic Biol Med*. 2023;208:672–683. doi:10.1016/j.freeradbiomed.2023.09.020
10. Shi R, Yang F, Wu H, et al. The Diagnostic Value of Liver Biopsy for Unexplained Liver Dysfunction: a Retrospective Study. *J Multidiscip Healthc*. 2024;17:2399–2407. doi:10.2147/JMDH.S460338
11. Perry IJ, Wannamethee SG, Shaper AG. Prospective study of serum gamma-glutamyltransferase and risk of NIDDM. *Diabetes Care*. 1998;21(5):732–737. doi:10.2337/diacare.21.5.732
12. Nakanishi N, Suzuki K, Tatara K. Serum gamma-glutamyltransferase and risk of metabolic syndrome and type 2 diabetes in middle-aged Japanese men. *Diabetes Care*. 2004;27(6):1427–1432. doi:10.2337/diacare.27.6.1427
13. Targher G. Elevated serum gamma-glutamyltransferase activity is associated with increased risk of mortality, incident type 2 diabetes, cardiovascular events, chronic kidney disease and cancer - A narrative review. *Clin Chem Lab Med*. 2010;48(2):147–157. doi:10.1515/CCLM.2010.031
14. Yahya R, Jainandunsing S, Rashid M, et al. HDL associates with insulin resistance and beta-cell dysfunction in South Asian families at risk of type 2 diabetes. *J Diabetes Complications*. 2021;35(10):107993. doi:10.1016/j.jdiacomp.2021.107993
15. Bardini G, Dicembrini I, Rotella CM, et al. Correlation between HDL cholesterol levels and beta-cell function in subjects with various degree of glucose tolerance. *Acta Diabetol*. 2013;50(2):277–281. doi:10.1007/s00592-011-0339-0
16. Xie W, Liu B, Tang Y, et al. Gamma-glutamyl transferase to high-density lipoprotein cholesterol ratio: a valuable predictor of type 2 diabetes mellitus incidence. *Front Endocrinol*. 2022;13:1026791. doi:10.3389/fendo.2022.1026791

17. Xepapadaki E, Nikdima I, Sagiadinou EC, et al. HDL and type 2 diabetes: the chicken or the egg. *Diabetologia*. 2021;64(9):1917–1926. doi:10.1007/s00125-021-05509-0
18. Lee SH, Kim HS, Park YM, et al. HDL-Cholesterol, Its Variability, and the Risk of Diabetes: a Nationwide Population-Based Study. *J Clin Endocrinol Metab*. 2019;104(11):5633–5641. doi:10.1210/jc.2019-01080
19. Xie Q, Lu S, Kuang M, et al. Assessing the longitudinal association between the GGT/HDL-C ratio and NAFLD: a cohort study in a non-obese Chinese population. *BMC Gastroenterol*. 2022;22(1):500. doi:10.1186/s12876-022-02598-y
20. Feng G, Feng L, Zhao Y. Association between ratio of γ-glutamyl transpeptidase to high-density lipoprotein cholesterol and prevalence of nonalcoholic fatty liver disease and metabolic syndrome: a cross-sectional study. *Ann Transl Med*. 2020;8(10):634. doi:10.21037/atm-19-4516
21. Li Q, Han Y, Hu H, et al. Gamma-glutamyl transferase to high-density lipoprotein cholesterol ratio has a non-linear association with non-alcoholic fatty liver disease: a secondary prospective cohort study in non-obese Chinese adults. *Front Med Lausanne*. 2022;9:995749. doi:10.3389/fmed.2022.995749
22. Hu H, Han Y, Guan M, et al. Elevated gamma-glutamyl transferase to high-density lipoprotein cholesterol ratio has a non-linear association with incident diabetes mellitus: a second analysis of a cohort study. *J Diabetes Investig*. 2022;13(12):2027–2037. doi:10.1111/jdi.13900
23. Zhao Y, Xin X, Luo XP. The relationship between the ratio of gamma-glutamyltransferase to high-density lipoprotein cholesterol and the risk of diabetes mellitus using publicly available data: a secondary analysis based on a longitudinal study in Japan. *Lipids Health Dis*. 2023;22(1):7. doi:10.1186/s12944-023-01772-9
24. Research Gate. Pharmacologic Approaches to Glycemic Treatment: standards of Care in Diabetes-2024. *Diabetes Care*. 2024;47:S158–158S178.
25. Li C, Zhang D, Pang X, et al. Trajectories of Perioperative Serum Tumor Markers and Colorectal Cancer Outcomes: a Retrospective, Multicenter Longitudinal Cohort Study. *EBioMedicine*. 2021;74:103706. doi:10.1016/j.ebiom.2021.103706
26. Burro R, Raccanello D, Pasini M, Brondino M. An Estimation of a Nonlinear Dynamic Process Using Latent Class Extended Mixed Models: affect Profiles After Terrorist Attacks. *Nonlin Dynam Psychol Life Sci*. 2018;22(1):35–52.
27. Whitfield JB. Gamma glutamyl transferase. *Crit Rev Clin Lab Sci*. 2001;38(4):263–355. doi:10.1080/20014091084227
28. Lee DH, DRM Gross, et al. Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Clin Chem*. 2003;49(8):1358–1366. doi:10.1373/49.8.1358
29. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature*. 2006;440(7086):944–948. doi:10.1038/nature04634
30. Matsuzawa-Nagata N, Takamura T, Ando H, et al. Increased oxidative stress precedes the onset of high-fat diet-induced insulin resistance and obesity. *Metabolism*. 2008;57(8):1071–1077. doi:10.1016/j.metabol.2008.03.010
31. Taylor R. Banting Memorial Lecture 2012 Reversing the twin cycles of Type 2 diabetes. *Diabet Med*. 2013;30(3):267–275. doi:10.1111/dme.12039
32. Kuchay MS, Krishan S, Mishra SK, et al. Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial). *Diabetologia*. 2020;63(11):2434–2445. doi:10.1007/s00125-020-05265-7
33. Jayachandran M, Qu S. Harnessing hyperuricemia to atherosclerosis and understanding its mechanistic dependence. *Med Res Rev*. 2021;41(1):616–629. doi:10.1002/med.21742
34. Athyros VG, Doumas M, Imprialos KP, et al. Diabetes and lipid metabolism. *Hormones*. 2018;17(1):61–67. doi:10.1007/s42000-018-0014-8
35. Drew BG, Duffy SJ, Formosa MF, et al. High-density lipoprotein modulates glucose metabolism in patients with type 2 diabetes mellitus. *Circulation*. 2009;119(15):2103–2111. doi:10.1161/CIRCULATIONAHA.108.843219
36. Sturek JM, Castle JD, Trace AP, et al. An intracellular role for ABCG1-mediated cholesterol transport in the regulated secretory pathway of mouse pancreatic beta cells. *J Clin Invest*. 2010;120(7):2575–2589. doi:10.1172/JCI41280
37. Rye KA, Barter PJ, Cochran BJ. Apolipoprotein A-I interactions with insulin secretion and production. *Curr Opin Lipidol*. 2016;27(1):8–13. doi:10.1097/MOL.0000000000000253
38. Cochran BJ, Manandhar B, Rye KA. HDL and Diabetes. *Adv Exp Med Biol*. 2022;1377:119–127.