

A Strong Interaction between Serum γ -Glutamyltransferase and Obesity on the Risk of Prevalent Type 2 Diabetes: Results from the Third National Health and Nutrition Examination Survey

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Background: Some studies have found an association of obesity with type 2 diabetes only among individuals with high normal serum γ -glutamyltransferase (GGT) activity, not in those with low serum GGT. If this interaction reflected pathophysiology, it would have scientific and clinical importance. The findings failed to reach statistical significance, however, and no articles have focused on the topic. We investigated possible interactions between serum GGT and body mass index (BMI) and their effects on the risk of prevalent type 2 diabetes and homeostasis model assessment (HOMA) insulin resistance.

Methods: We analyzed 4011 adults ≥ 40 years old who participated in the 3rd US National Health and Nutrition Examination Survey.

Results: BMI was associated with prevalent diabetes only among persons with high normal serum GGT activity (P for interaction = 0.002). In the highest serum GGT quartile, adjusted odds ratios for BMI 25–29.9, 30–34.5, and ≥ 35 kg/m² compared with BMI < 25 kg/m² were 3.1, 5.1, and 6.2, respectively (P for trend < 0.001). In the lowest serum GGT quartile, BMI was not associated with diabetes; corresponding adjusted odds ratios were 1.0, 0.9, 1.8, and 0.8 (P for trend = 0.551). After prevalent diabetes was excluded, there was a parallel interaction with HOMA levels (P for interaction < 0.001).

Conclusions: BMI was not associated with prevalent type 2 diabetes when GGT was low normal, suggesting

that obesity itself may not be a sufficient risk factor for type 2 diabetes. Practically, this interaction can be useful in clinical settings to identify individuals at high risk for type 2 diabetes.

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Although increased serum γ -glutamyltransferase (GGT)⁴ has been regarded as a biomarker of hepatobiliary disease and alcohol consumption, cellular GGT is an ectoplasmic enzyme responsible for the extracellular catabolism of glutathione and is widely distributed in various cells with high secretory or absorptive activities (1).

Recent population-based epidemiological studies have shown a strong association of serum GGT activities within the reference interval with many cardiovascular disease risk factors or components of metabolic syndrome (2–14). In addition, in prospective studies, baseline serum GGT activity predicted future diabetes, hypertension, stroke, and myocardial infarction (3–14). Among these diseases, serum GGT within the reference interval most strongly predicted incident type 2 diabetes (5, 8–13).

Recently, the prevalence and incidence of type 2 diabetes have increased alarmingly worldwide and across all age, sex, and race/ethnic groups (15). Although obesity is undoubtedly an important risk factor for type 2 diabetes (16), some prospective cohort studies (8–10, 13) [with the exception of male participants in study (13)] found that the association of obesity with the risk of type 2 diabetes may be weak to nonexistent in individuals with low normal serum GGT but strong in those with high normal serum GGT. For example, in Korean men (8), incidence rates of type 2 diabetes were 0.4%, 0.8%, and 2.6% across

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⁴ Nonstandard abbreviations: GGT, γ -glutamyltransferase; BMI, body mass index; HOMA, homeostasis model assessment; NHANES, National Health and Nutrition Examination Survey; ALT, alanine aminotransferase; POP, persistent organic pollutant.

categories of body mass index (BMI) among study participants with serum GGT <20 U/L, whereas corresponding rates were 0%, 5.4%, and 22.7% among those with serum GGT >40 U/L. Like BMI, age was a strong risk factor for diabetes only among individuals with high normal GGT in a prospective cohort study of Asian men (8), but this pattern of findings was not replicated in other prospective cohort studies (9, 10).

Although the reported interactions of obesity and GGT received little attention, perhaps because they failed to reach statistical significance, the interaction of obesity and GGT is scientifically important if it indicates that obesity may not be a sufficient cause for developing type 2 diabetes. Confirmation of this finding could simplify diabetes screening, because overweight and obese people with low normal GGT would no longer be considered at high risk.

Given the potential scientific importance of an interaction between obesity and GGT in predicting diabetes, replication and careful analysis focused on the interaction itself is needed. Therefore, we investigated whether the associations of obesity or age with type 2 diabetes differed according to serum GGT activities. In addition, we examined the interactions with the homeostasis model assessment (HOMA) estimate of insulin resistance after excluding prevalent diabetes cases. Insulin resistance, often a diabetes precursor, was included as a 2nd dependent variable as a marker of consistency of the findings.

Materials and Methods

The National Health and Nutrition Examination Survey (NHANES) was conducted in the US from 1988 to 1994 by the National Center for Health Statistics of the CDC. The study population comprised complex, multistage, clustered samples of civilian, noninstitutionalized individuals at least 2 months old. A detailed description of survey methods and data collection procedures has been published (17).

MEASUREMENTS

The NHANES data collection included a standardized home interview followed by a detailed physical examination in a mobile evaluation clinic or in the participant's home. Information on a wide variety of sociodemographic, health behavior, medical, nutritional, and family history questions, including self-reported age, race/ethnicity, sex, history of smoking, alcohol consumption, and physical activity, was obtained during the home interview. The study protocol was reviewed and approved by the CDC institutional review board; additionally, informed written consent was obtained from all individuals before they took part in the study.

Venous serum and plasma were collected into EDTA tubes and shipped weekly at -20°C . Serum GGT activity was assayed with a Hitachi 737 Analyzer (Boehringer-Mannheim Diagnostics) at White Sands Research Center.

Plasma glucose concentration was measured with an enzymatic reaction, and insulin was measured by RIA.

EXCLUSION

Fasting blood specimens were obtained from 11 448 participants ≥ 40 years old. We excluded 4467 participants with missing data for serum GGT, glucose, insulin, BMI, cigarette smoking, alcohol consumption, or leisure time physical activity. We also excluded 2334 participants who had fasted fewer than 8 h, and 3 women who were pregnant. The sample for our analysis included 4011 participants.

STATISTICAL ANALYSIS

Participants were considered to have diabetes mellitus if their fasting plasma glucose was 7.0 mmol/L, they were taking insulin or a hypoglycemic agent, or they reported a history of diabetes diagnosed by a physician. To enhance our ability to remove confounding due to lifestyle changes typically made after a diagnosis of diabetes, including weight loss, we studied newly recognized diabetes as 1 endpoint (that is, we deleted previously known diabetics from the analysis). The HOMA estimate of insulin resistance was calculated as follows: fasting plasma insulin (mU/L) \times fasting plasma glucose (mmol/L)/22.5.

We used multiple logistic regression to examine the interaction relationships with prevalent diabetes as the dependent variable, predicted from either BMI (<25, 25–29.9, 30–34.9, and ≥ 35 kg/m²) or age (40–49, 50–59, 60–69, and ≥ 70 years) within 4 quartiles of GGT (<16, 17–22, 23–35, and ≥ 36 U/L). Next, we used linear regression to examine interaction models with HOMA as the dependent variable and the same independent variables used for logistic regressions, after excluding the 578 prevalent diabetes cases. Adjusting variables were race/ethnicity, sex, poverty income ratio, smoking status (never smoker, exsmoker, and current smoker), alcohol intake (frequency of drinking beer, wine, or liquor per month), and leisure time physical activity (created by summing the products of the frequency of participation by metabolic equivalent levels for each reported activity). All statistical analyses were performed with SAS 9.1 and SUDAAN 9.0 and accounted for correlations within primary sampling units. Our stratified models were adjusted for age, race/ethnicity, and poverty income ratio, adjustments regarded as a good compromise between efficiency and bias (18, 19); therefore we did not use sampling weights.

Results

The study population included 578 patients with prevalent diabetes and 205 with newly recognized diabetes. Although the marginal association of BMI with prevalent diabetes was strong, the association varied by serum GGT activity (Table 1). As serum GGT activity increased, the association between BMI and prevalent diabetes strength-

Table 1. Adjusted^a odds ratios (ORs) and 95% CI of prevalent diabetes by category of BMI after stratification by quartile of serum GGT (*P* for multiplicative interaction = 0.004).

	BMI, kg/m ²				<i>P</i>
	<25	25–29.9	30–34.9	≥35	
All study participants					
Case/no. of participants	105/1316	224/1540	158/770	91/385	
Prevalence, %	8.0%	14.6%	20.5%	23.6%	
Adjusted OR (95% CI)	Reference	2.0 (1.6–2.6)	3.4 (2.6–4.5)	4.5 (3.0–6.8)	<0.001
Stratified by serum GGT					
<16 U/L					
Case/no. of participants	26/455	17/341	11/119	2/49	
Prevalence, %	5.7%	5.0%	9.2%	4.1%	
Adjusted OR (95% CI)	Reference	0.9 (0.5–1.7)	1.8 (0.8–4.6)	0.8 (0.2–4.1)	0.551
17–22 U/L					
Case/no. of participants	28/337	51/385	21/178	12/102	
Prevalence, %	8.3%	13.3%	11.8%	11.8%	
Adjusted OR (95% CI)	Reference	1.6 (0.9–2.9)	1.6 (0.9–3.1)	1.7 (0.7–4.2)	0.139
23–35 U/L					
Case/no. of participants	27/268	65/417	59/254	34/113	
Prevalence, %	10.1%	15.6%	23.2%	30.1%	
Adjusted OR (95% CI)	Reference	1.7 (1.1–2.6)	3.2 (1.8–5.8)	4.7 (2.2–10.3)	<0.001
≥36					
Case/no. of participants	24/256	91/397	67/219	43/121	
Prevalence, %	9.4%	22.9%	30.6%	35.5%	
Adjusted OR (95% CI)	Reference	3.1 (1.8–5.3)	5.1 (2.8–9.1)	6.2 (3.0–12.9)	<0.001

^a Multiple logistic regression, adjusted for age, sex, race/ethnicity, poverty income ratio, cigarette smoking, leisure time physical activity, and alcohol consumption.

ened ($P = 0.002$ for multiplicative interaction). For example, within the lowest quartile of serum GGT, BMI was not associated with prevalent diabetes, in contrast to the highest quartile of serum GGT, wherein adjusted odds ratios for prevalent diabetes were 1.0, 3.1, 5.1, and 6.2 (P for trend <0.001). The interaction was more clearly shown with newly recognized diabetes cases (Fig. 1; note that quartiles 1 and 2 of serum GGT were merged given small numbers of newly recognized events). The pattern of event rates in Table 1 and Fig. 1 also indicated that the association between serum GGT and diabetes became stronger as BMI increased and that serum GGT was positively associated with diabetes even among patients with BMI <25 kg/m². When we analyzed waist circumference instead of BMI, a similar interaction with serum GGT was observed (data not shown).

After prevalent diabetes was excluded, an interaction that affected HOMA levels also occurred between BMI and serum GGT activity (Fig. 2). The association between BMI and HOMA became stronger at higher serum GGT activity (P for additive interaction <0.001).

Although serum GGT had a high correlation of 0.51 with another liver enzyme, serum alanine aminotransferase (ALT), serum ALT did not show any interaction with

BMI in prediction of diabetes; the nonsignificant estimate of interaction was further attenuated after adjustment for serum GGT (data not shown). After adjustment for serum ALT (data not shown), however, the interaction of BMI and serum GGT that enabled estimation of prevalent diabetes persisted.

The association of age with diabetes was not indicated by differences in serum GGT activity (Table 2; P for multiplicative interaction = 0.12). Similarly, no GGT interaction was seen for age in relation to either newly recognized diabetes or HOMA (data not shown).

In exploratory analyses to detect interactions that may enable prediction of prevalent or newly recognized diabetes, we examined possible interactions of BMI with other clinical variables, including serum antioxidant vitamins (vitamin C or carotenoid), inflammation markers (C-reactive protein), or serum lipids (LDL-cholesterol or triglyceride). No interaction was identified (data not shown).

Discussion

This study found that the association of obesity with the prevalence of type 2 diabetes varied with serum GGT activity; BMI was associated with prevalent diabetes only

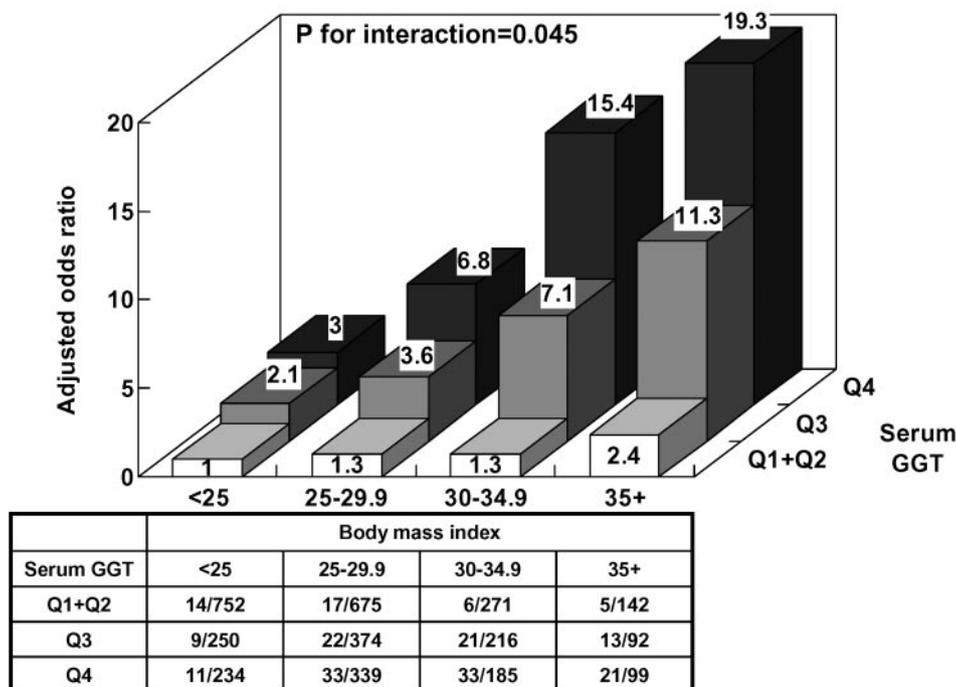


Fig. 1. Adjusted odds ratios (ORs) and 95% CIs of newly recognized diabetes (205 cases) by category of BMI and quartiles (Q) of serum GGT.

Numbers in the table are the numbers of cases and individuals at risk in each category. ORs were adjusted for age, sex, race/ethnicity, poverty income ratio, cigarette smoking, leisure time physical activity, and alcohol consumption; all ORs were calculated with the reference group of subjects with lowest category of both BMI and serum GGT. First and 2nd quartiles of serum GGT were combined because of small numbers of cases of newly recognized diabetes.

when GGT was in its high normal range. In patients with low normal serum GGT activity, BMI was not associated with diabetes. Although these data were cross-sectional, this study was performed to further investigate and confirm the limited findings concerning this interaction in prospective cohort studies (8–10, 13). The consistency of the finding for related outcome variables (newly recognized diabetes and HOMA in patients without prevalent diabetes) adds inferential strength, because participants who do not know they have diabetes cannot take lifestyle measures (such as weight loss, increased physical activity, or diet change) in response to diabetes.

All epidemiological studies to date on serum GGT have focused on the main associations of serum GGT with various disease outcomes, including diabetes (3–7, 11, 12, 14). Three prospective cohort studies (8–10), however, investigated BMI subgroups and found an interaction, not statistically significant, in which obesity was weakly associated with incident diabetes in people with low normal serum GGT but strongly associated in those with high normal serum GGT. One possible interpretation of this interaction, if it did not arise by chance, is that obese individuals with high normal GGT have already suffered subclinical pathological changes attributable to obesity, whereas obese individuals with low normal GGT are at an earlier stage of pathogenesis. In this interpretation, serum GGT activity is an intervening factor in the association between obesity and diabetes. If this were true, adjustment for GGT should have substantially attenuated the association between BMI and type 2 diabetes; however, adjustment for GGT (ignoring interaction) did not materially change the association between BMI and the risk of type 2 diabetes in either the present cross-sectional or

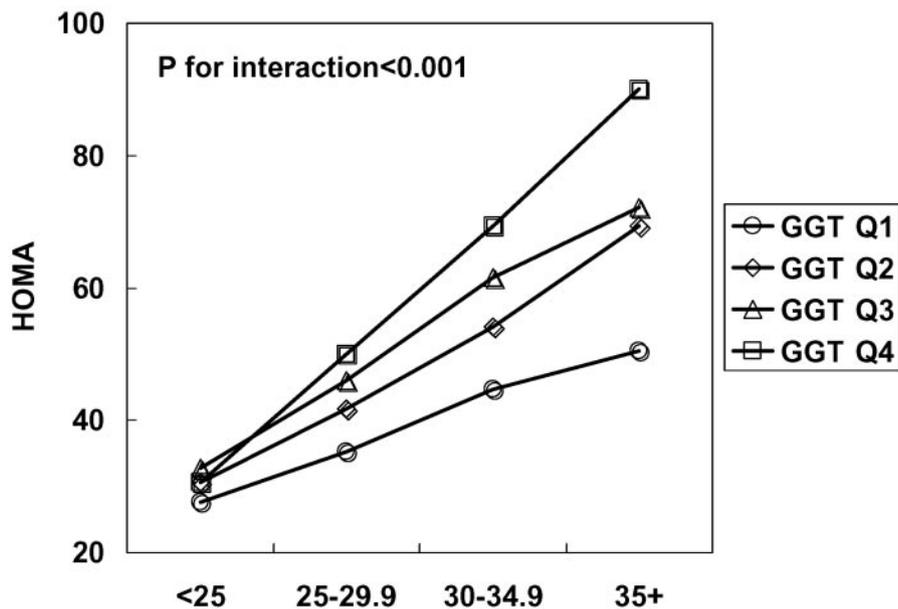
previous cohort studies, and in fact, an interaction model appears to be a better fit to the data than does the simple adjustment model.

An interaction between BMI and GGT on type 2 diabetes could be important both scientifically and clinically. The most interesting scientific finding was that BMI was not associated with type 2 diabetes among individuals with low normal GGT. This finding suggests that obesity itself may not be a sufficient risk factor for type 2 diabetes. Rather, in this view, to be a risk factor for diabetes, obesity must be coupled with other factors, such as those associated with increased serum GGT. In this context, one suggestion has been that fatty liver disease, such as nonalcoholic steatohepatitis, can explain the current finding because fatty liver may be related to obesity, serum GGT, and type 2 diabetes (20). Serum ALT is a more sensitive marker of fatty liver than is GGT (21), however, and we observed no BMI and serum ALT interaction associated with prevalent diabetes. The interaction of diabetes prevalence and BMI with GGT was specific; no interaction was seen with age or several other clinical variables representing antioxidants, inflammation, and serum lipids.

Interestingly, in our recent study of the NHANES dataset in which we observed a striking dose-response relation between serum concentrations of persistent organic pollutants (POPs; endocrine disruptors) and prevalence of diabetes (22), we also observed an interaction between POPs and BMI on the risk of diabetes, parallel to the findings of current study. The primary source for exposure in the general population is through the diet, especially fatty animal foods. In that study, the association between obesity and diabetes became stronger as

Fig. 2. Adjusted geometric means of HOMA by category of BMI and quartiles (Q) of serum GGT after excluding prevalent diabetes (P for interaction <0.001).

Numbers in the table are the numbers of individuals in each category. Linear regression was adjusted for age, sex, race/ethnicity, poverty income ratio, cigarette smoking, leisure time physical activity, and alcohol consumption.



Serum GGT	Body mass index			
	<25	25-29.9	30-34.9	35+
Q1	429	324	108	47
Q2	309	334	157	90
Q3	241	352	195	79
Q4	232	306	152	78

serum concentrations of POPs increased. Obesity was not associated with diabetes among individuals with very low concentrations of POPs, in whom the prevalence of diabetes itself was quite low. We interpreted these observations as suggesting that POPs contained in the adipose tissue, not obesity itself, may play a key role in the pathogenesis of diabetes. A related important finding is a dose-response relation between serum concentrations of POPs and serum GGT in the same NHANES dataset (23); as serum concentrations of POPs increased, serum GGT also increased. In that study (23), we interpreted serum GGT within its reference range as a general marker of exposure to various environmental xenobiotics that are metabolized by glutathione conjugation, including both diabetes-related xenobiotics, such as POPs, and other compounds unrelated to diabetes (23). It is possible that recently reported associations between serum GGT and various health outcomes (2-14) may be explained by increases in serum GGT due to the exposure to various environmental pollutants. Taken together, findings linking serum GGT, POPs, obesity, and diabetes could be interpreted as indicating that obesity can increase the risk of type 2 diabetes only in the presence of diabetogenic environmental xenobiotics, which are associated with increased serum GGT.

On the other hand, the current findings may be useful in the clinical or research setting, whatever pathophysio-

logic mechanism underlies the interaction between BMI and GGT and its association with diabetes. Characterization of the interaction between BMI and GGT may help to define a high-risk target population in which timely intervention may prevent development of type 2 diabetes while allowing for less screening attention applied to obese people who have low normal GGT. Such a clinical application may become more useful as the proportion of obese persons increases among the total population.

This study has several limitations. The current findings must be interpreted with caution because of the cross-sectional study design. The possibility of reverse causality is lessened, however, because similar findings were shown in several prospective studies and the findings of the present study were confirmed by the outcomes for newly recognized diabetes and HOMA. Another limitation is that the NHANES dataset did not allow us to differentiate type 1 from type 2 diabetes. Because we restricted the study to participants >40 years old, however, the majority of diabetic cases were likely to be type 2. When we further restricted the study to participants >60 years old or combined the 2 categories of BMI (<25 and 25-29.9), similar relations were observed. In addition, in people >40 years old, the number of individuals belonging to the category of low normal serum GGT who did not show a significant relation between obesity and diabetes was $\sim 50\%$ the total study participants, and the

Table 2. Adjusted^a odds ratios (ORs) and 95% CI of prevalent diabetes by category of age after stratification by quartiles of serum GGT (*P* for interaction = 0.100).

	Age, years				<i>P</i> trend
	40–49	50–59	60–69	≥70	
All study participants					
Case/no. of participants	83/1128	107/765	169/908	219/1210	
Prevalence, %	7.4%	14.0%	18.6%	18.1%	
Adjusted OR	Reference	2.2	3.2	4.0	<0.001
(95% CI)		(1.6–2.9)	(2.3–4.5)	(3.0–5.2)	
Stratified analysis by serum GGT					
<16 U/L					
Case/no. of participants	5/280	3/157	16/183	32/344	
Prevalence, %	1.8%	1.9%	8.7%	9.3%	
Adjusted OR	Reference	1.2	5.5	6.9	<0.001
(95% CI)		(0.2–6.6)	(1.5–19.8)	(2.6–18.2)	
17–22 U/L					
Case/no. of participants	16/233	11/187	24/215	61/367	
Prevalence, %	6.9%	5.9%	11.2%	16.6%	
Adjusted OR	Reference	0.9	1.7	2.8	<0.001
(95% CI)		(0.4–2.0)	(1.0–3.1)	(1.6–5.1)	
23–35 U/L					
Case/no. of participants	21/294	40/206	56/257	68/295	
Prevalence, %	7.1%	19.4%	21.8%	23.1%	
Adjusted OR	Reference	3.2	4.2	5.2	<0.001
(95% CI)		(1.9–5.5)	(2.2–8.0)	(3.2–8.6)	
≥36					
Case/no. of participants	41/321	53/215	73/253	58/204	
Prevalence, %	12.8%	24.7%	28.9%	28.4%	
Adjusted OR	Reference	2.3	2.9	3.6	<0.001
(95% CI)		(1.4–3.7)	(1.8–4.7)	(2.2–5.8)	

^a Logistic Logistic regression adjusted for age, sex, race/ethnicity, poverty income ratio, cigarette smoking, leisure time physical activity, and alcohol consumption.

number of diabetes cases was 168. Thus, it seems quantitatively improbable that the lack of association between obesity and diabetes among those with low normal serum GGT is attributable to a few patients with type 1 diabetes who were not obese or insulin resistant. The final limitation to be addressed is that patients in the newly recognized diabetes group included those who had had hyperglycemia for several years before it was discovered or diagnosed. When we examine the association between BMI and diabetes, however, whether patients knew that they had diabetes or not may be important because knowing about diabetes can lead to changes in behaviors and body weight. To guard against this type of bias, common in cross-sectional analyses, we analyzed the 3 outcomes of all diabetes, newly recognized diabetes, and HOMA-IR; all of them were consistent.

In summary, our analysis of the NHANES III study participants revealed an interaction between BMI and serum GGT that was associated with the risk of prevalent diabetes. These findings indicate that obesity itself may not be a sufficient risk factor for type 2 diabetes; obesity may enhance the risk of type 2 diabetes in the presence of diabetogenic xenobiotics. Clinically or in case findings,

the interaction between BMI and serum GGT may be useful for detecting a high-risk subpopulation of type 2 diabetes.

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