

Elevated Liver Function Enzymes Are Related to the Development of Prediabetes and Type 2 Diabetes in Younger Adults

The Bogalusa Heart Study

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OBJECTIVE—Elevations in alanine aminotransferase (ALT) and γ -glutamyl transferase (GGT), surrogate markers of liver dysfunction and nonalcoholic fatty liver, are considered as part of metabolic syndrome and related type 2 diabetes. However, information is limited regarding the long-term predictability of ALT and GGT in the development of prediabetes and type 2 diabetes.

RESEARCH DESIGN AND METHODS—In this retrospective cohort study, normoglycemic ($n = 874$), prediabetic ($n = 101$), and diabetic ($n = 80$) adults aged 26–50 years (average age 41.3 years) were followed over an average period of 16 years since their young adulthood (aged 18–38 years, average age 25.1 years), with measurements of cardiometabolic risk factor variables including ALT and GGT.

RESULTS—The follow-up prevalence rate of adult diabetes status by quartiles of baseline ALT and GGT levels showed an adverse trend for both prediabetes ($P < 0.05$) and diabetes ($P < 0.01$). In a longitudinal multivariate logistic regression analysis that included anthropometric, hemodynamic, and metabolic variables, as well as alcohol consumption and smoking, individuals with elevated baseline ALT and GGT levels (per 1-SD increment) were 1.16 and 1.20 times, respectively, more likely to develop diabetes ($P = 0.05$ for ALT and $P < 0.01$ for GGT); no such associations were noted for prediabetes. Regarding the predictive value of ALT and GGT, the area under the receiver operating curve analysis yielded C values ranging from 0.70 to 0.82, with values significantly higher for diabetes compared with prediabetes.

CONCLUSIONS—These findings in younger adults suggest potential clinical utility of including ALT and GGT as biomarkers in diabetes risk assessment formulations.

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Impaired glucose homeostasis is one of the most common causes of death in the U.S. (1). The progressive global epidemic of obesity has resulted in obesity being a major causal factor for prediabetes and type 2 diabetes (2,3). In addition, obesity-related nonalcoholic fatty liver disease (NAFLD) has reached epidemic proportions and has become the most common cause of chronic liver disease

in Westernized populations (4). Increased activities of liver enzymes such as alanine aminotransferase (ALT) and γ -glutamyl transferase (GGT) are considered early surrogate markers of NAFLD (4,5). Studies also indicate that elevated activities of these enzymes are associated with metabolic syndrome and related clinical manifestations including cardiovascular disease and type 2 diabetes (4–11).

Most studies of liver function enzymes related to metabolic syndrome and incident type 2 diabetes are mainly limited to middle- and older-aged populations (6–10). As part of the Bogalusa Heart Study, a biracial (black–white) community-based investigation of the early natural history of cardiovascular disease (12), the current study examines the association and potential predictability of ALT and GGT for the onset of type 2 diabetes in apparently healthy younger adults.

RESEARCH DESIGN AND METHODS

Study population

The Bogalusa Heart Study is being conducted in the semirural, biracial (65% white and 35% black) community of Bogalusa, Louisiana. Between 1985 and 1996, three cross-sectional surveys of younger adults were conducted (baseline surveys). In addition, four cross-sectional surveys of subjects who had been previously examined were conducted between 1997 and 2010 (follow-up surveys). A total of 1,055 fasting subjects (72% white; 40% male) were selected from the last four surveys (1997–2010) of adults to form a retrospective cohort for this study. At baseline examination, individuals with a history of treatment for diabetes or those with a fasting glucose level ≥ 100 mg/dL were excluded. At the initial screening, the mean (SD) age was 25.1 (4.0) years (range, 18–38 years). At the most recent screening, the mean age was 41.3 (5.1) years (range, 26–50 years). The mean follow-up interval was 16.2 (4.9) years. The number of screenings and follow-up visits since young adulthood ranged from two to seven times. In all, 84% of subjects were screened three or more times and 74% were screened three to five times, with a total of 4,135 observations.

On the basis of data from the follow-up surveys, adult subjects were classified as normoglycemic, prediabetic, or diabetic

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according to American Diabetes Association criteria (13). Individuals with a fasting glucose level of 99 mg/dL or lower were considered normoglycemic ($n = 874$), those with a fasting glucose level between 100 and 125 mg/dL were considered prediabetic ($n = 101$), and subjects with a fasting glucose level of 126 mg/dL or higher or who had a history of treatment for the condition were considered diabetic ($n = 80$). All participants provided informed consent, and the institutional review board of the Tulane University Health Sciences Center approved the study.

General examination

Identical protocols were used by trained examiners across all surveys (14). Briefly, subjects were instructed to fast overnight (at least 8 h) before the screening, with compliance ascertained by interview on the day of examination. Information on personal health and medication history were obtained by questionnaires. Anthropometric and blood pressure measurements were collected in replicate and mean values were used. BMI (calculated as weight in kilograms divided by height in meters squared) was used as a measure of overall adiposity. Blood pressure measurements were obtained using the right arm of the subjects in a relaxed, sitting position. Systolic and diastolic blood pressures were recorded at the first and fifth Korotkoff phases using a mercury sphygmomanometer. Mean arterial pressure (MAP) was calculated as diastolic blood pressure plus one-third pulse pressure. Individuals were considered smokers if they reported currently smoking or having stopped smoking only within the past year. In a similar manner, individuals were considered alcohol drinkers if they reported current consumption of alcohol or having stopped alcohol drinking only within the past year.

Laboratory analyses

From 1973 to 1986, cholesterol and triglyceride levels were measured using chemical procedures on a Technicon Autoanalyzer II (Technicon Instrument Corporation, Tarrytown, NY), according to the laboratory manual of the Lipid Research Clinics Program. These variables were later determined by enzymatic procedures on the Abbott VP instrument (Abbott Laboratories, North Chicago, IL) between 1987 and 1996 and on the Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, IN) afterward.

Both chemical and enzymatic procedures met the performance requirements of the Lipid Standardization Program of the Centers for Disease Control and Prevention, which has routinely monitored the precision and accuracy of cholesterol, triglyceride, and HDL cholesterol measurements since the beginning of this study. Serum lipoprotein cholesterol were analyzed using a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures (15). The intraclass correlation coefficients between the blind duplicate (10% random sample) values ranged from 0.86 to 0.98 for HDL cholesterol, 0.86 to 0.98 for LDL cholesterol, and 0.88 to 0.99 for triglycerides. Glucose, ALT, and GGT were measured as part of a multichemistry profile (SMA20) by enzymatic procedures using the multi-channel Olympus Au-5000 Analyzer (Olympus, Lake Success, NY). Plasma immunoreactive insulin levels were measured by a commercial radioimmunoassay kit (Phadebas; Pharmacia Diagnostics, Piscataway, NJ). The intraclass correlation coefficients between blind duplicate values ranged from 0.94 to 0.98 for insulin, 0.86 to 0.98 for glucose, 0.97 for ALT, and 0.99 for GGT. In addition, an index of insulin resistance was calculated according to the homeostasis model assessment of insulin resistance (HOMA-IR) equation (16):

$$\text{HOMA-IR} = [\text{insulin (microunits per milliliter)} \times \text{glucose (millimoles per liter)}] / 22.5$$

Statistical analysis

All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC). In the analyses, since there was no interaction between race (or sex) with liver function enzyme variables (ALT and GGT), the race and sex groups were combined to increase statistical power and to simplify the presentation. Continuous variables were tested for normality using a Kolmogorov-Smirnov test. Values of triglycerides, glucose, insulin, and insulin resistance index (HOMA-IR) were log transformed to improve normality, as applicable. General linear models were used to examine the cardiometabolic risk factor variables by status of adult diabetes, adjusted for age, race, and sex. The trends of follow-up diabetes by baseline ALT and GGT quartile levels were examined using the Cochran-Armitage trend test.

Longitudinal multivariate logistic regression analyses (generalized equation estimation method) were used to determine which longitudinal changes in risk variables since baseline predicted follow-up adult diabetes status. Risk variables were standardized to z scores based on age-, race-, and sex-specific means and SDs. The model included smoking (yes/no)

Table 1—Risk factors and cardiometabolic characteristics of individuals within the fasting normoglycemic range at baseline according to their diabetes status at follow-up: the Bogalusa Heart Study

Baseline variable	Normoglycemia	Prediabetes	Diabetes
<i>n</i>	874	101	80
Age (years) ^a	25.0 ± 3.9	25.7 ± 4.4	25.6 ± 4.6
BMI (kg/m ²) ^b	24.7 ± 5.4	26.1 ± 5.6	30.6 ± 7.3****
Systolic BP (mmHg) ^b	109.7 ± 10.0	115.3 ± 11.6****	114.4 ± 11.9***
Diastolic BP (mmHg) ^b	70.9 ± 8.1	73.5 ± 8.3	73.6 ± 9.8*
MAP (mmHg) ^b	83.8 ± 8.1	87.4 ± 8.9**	87.2 ± 9.8**
HDL cholesterol (mg/dL) ^b	51.5 ± 17.5	48.2 ± 18.9	47.1 ± 17.0**
LDL cholesterol (mg/dL) ^b	114.8 ± 32.9	122.3 ± 32.6*	127.4 ± 31.6****
Triglycerides (mg/dL) ^b	103.1 ± 65.9	102.5 ± 48.3	137.6 ± 83.5****
Glucose (mg/dL) ^b	80.0 ± 7.6	85.4 ± 7.2****	84.5 ± 7.5****
Insulin (μU/mL) ^b	10.5 ± 8.4	12.3 ± 8.8*	17.2 ± 11.8****
HOMA-IR ^b	2.1 ± 1.9	2.6 ± 2.0**	3.6 ± 2.5****
Smoking (%) ^b	44.6	39.8	39.4
Alcohol drinking (%) ^b	59.5	69.7	59.2
ALT (U/L) ^b	22.4 ± 16.3	29.1 ± 21.9*	27.1 ± 21.1**
GGT (U/L) ^b	20.6 ± 29.3	23.6 ± 21.6	23.9 ± 18.7*

Data are mean ± SD and based on first measurement at baseline. SI conversion factors: To convert the values for glucose to millimoles per liter, divide by 18; cholesterol to millimoles per liter, multiply by 0.02586; triglycerides to millimoles per liter, multiply by 0.01129; and insulin to picomoles per liter, multiply by 6. BP, blood pressure. ^a*P* values were adjusted for race and sex. ^b*P* values were adjusted for age, race, and sex. **P* < 0.05 vs. normoglycemia. ***P* < 0.01 vs. normoglycemia. ****P* < 0.001 vs. normoglycemia. *****P* < 0.0001 vs. normoglycemia.

and alcohol drinking (yes/no) observed since baseline as longitudinal categorical variables and BMI, MAP, HDL cholesterol, LDL cholesterol, triglycerides, and HOMA-IR as longitudinal continuous variables, as well as ALT and GGT (model 1 and 2, respectively), adjusted for study year, age, age squared, race, sex, and sex by race interaction, as applicable. Odds ratios are expressed per 1-SD increment in BMI, MAP, HDL cholesterol, LDL cholesterol, triglycerides, HOMA-IR, ALT, and GGT. Non-significant terms ($P > 0.05$) were removed from the model by backward stepwise procedure. To evaluate the discriminatory capability of the models using the area under the receiver operating characteristic (ROC) curve (C statistic), the multivariate C statistic logistic regressions were performed on the association of the baseline liver function enzymes and glucose homeostasis variables (glucose, insulin, and HOMA-IR) with prediabetes or diabetes status at the follow-up in adulthood adjusted for age, race, sex, smoking, drinking, BMI, MAP, HDL cholesterol, LDL cholesterol, and triglycerides. ROCs (C values) were tested for equality by diabetes status and by pairwise comparison of each model with the rest.

RESULTS—Mean levels of anthropometric, hemodynamic, metabolic, and liver function enzyme variables at baseline are presented in Table 1 by follow-up diabetes status. The prediabetic group, versus the normoglycemic group, displayed significantly higher systolic blood pressure, MAP, LDL cholesterol, glucose, insulin, HOMA-IR, and ALT. The diabetic group, versus the normoglycemic group, displayed higher BMI, systolic blood pressure, diastolic blood pressure, MAP, LDL cholesterol, triglycerides, glucose, insulin, HOMA-IR, ALT, and GGT and lower HDL cholesterol.

The follow-up prevalence rate of diabetes status after a 16-year interval by quartiles of baseline ALT and GGT is shown in Fig. 1. Significant adverse trends of ALT and GGT were noted for both prediabetic ($P < 0.01$) and diabetic ($P < 0.05$) groups.

Table 2 shows the results of a multivariable adjusted longitudinal logistic regression model that included BMI, MAP, HDL cholesterol, LDL cholesterol, triglycerides, and HOMA-IR along with ALT (model 1) and GGT (model 2) as a multiple repeated-measurement standardized variable (z scores) and smoking (yes/no) and alcohol drinking (yes/no) as a longitudinal repeated-measurement categorical variable

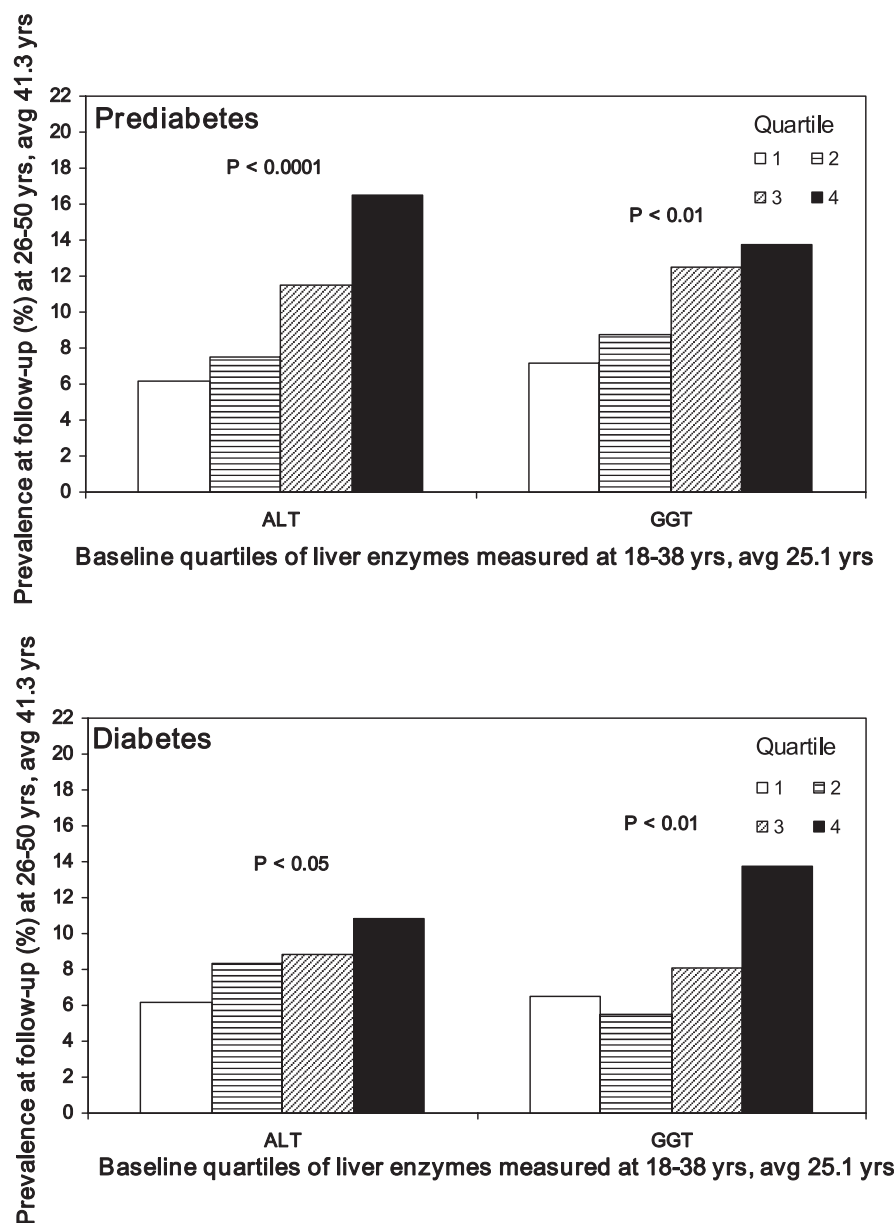


Figure 1—Prevalence of follow-up diabetes status by quartiles of baseline ALT and GGT levels in the Bogalusa Heart Study. ALT and GGT values by quartiles were <13.0 UI/L and <10 UI/L for quartile 1; from 13 to 18 UI/L and 10 to 14 UI/L for quartile 2; from 19 to 28 UI/L and 15 to 22 UI/L for quartile 3; and from 29 to 126 UI/L and 23 to 476 UI/L for quartile 4, respectively.

observed since baseline. After adjusting for study year, age, race, sex, and race by sex interaction (as applicable), expressed per 1-SD increase, HOMA-IR showed a significant odds ratio of 1.70 ($P < 0.0001$) for developing follow-up prediabetes after an average of 16 years of follow-up. Neither ALT nor GGT showed significant odds ratios in this regard. With respect to developing follow-up diabetes, the odds ratios per 1-SD increase were 1.16 ($P = 0.05$) for ALT and 1.20 ($P < 0.01$) for GGT. BMI, triglycerides, and HOMA-IR displayed

odds ratios of 1.77, 1.26, and 1.57, respectively ($P < 0.05$); BMI and triglycerides showed odds ratios of 2.23 and 1.36, respectively, in model 2 ($P < 0.001$). No significant race difference in the predictive value of liver function enzymes was observed for either prediabetes or diabetes (data not shown).

In terms of discriminative values of different baseline liver function enzymes and glucose homeostasis variables (glucose, insulin, and HOMA-IR) (Table 3), the predictive models produced C values

Table 2—Multivariate prediction of follow-up diabetes status according to baseline liver function enzymes and other cardiometabolic risk variables in the Bogalusa Heart Study cohort

Independent variable	Prediabetes vs. normoglycemia		Diabetes vs. normoglycemia	
	OR* (95% CI)	P value	OR* (95% CI)	P value
Model 1				
BMI	—		1.77 (1.37–2.28)	<0.0001
Triglycerides	—		1.26 (1.04–1.53)	<0.05
HOMA-IR	1.70 (1.42–2.04)	<0.0001	1.57 (1.23–2.01)	<0.001
ALT	0.96 (0.81–1.14)	0.654	1.16 (1.00–1.35)	0.05
Model 2				
BMI	—		2.23 (1.83–2.73)	<0.0001
Triglycerides	—		1.36 (1.16–1.60)	0.0002
HOMA-IR	1.69 (1.41–2.03)	<0.0001	—	
GGT	0.99 (0.81–1.22)	0.950	1.20 (1.06–1.35)	<0.01

Model includes smoking (yes/no), alcohol drinking (yes/no), BMI, MAP, HDL cholesterol, LDL cholesterol, triglycerides, and HOMA-IR, as well as ALT and GGT z scores (models 1 and 2, respectively) since baseline. Dashes signify did not retain in the model; OR, odds ratio. *Longitudinal logistic regression model with generalized equation estimation method, adjusted for study year, age, age squared, race, and sex, and the race × sex interaction, as applicable. ORs are expressed per 1-SD increment in BMI, triglycerides, HOMA-IR, ALT, and GGT z scores.

ranging from 0.701 to 0.751 and from 0.814 to 0.830 for prediabetes and diabetes for these measures, respectively, which were relatively similar to each other in magnitude. Compared with the prediabetic group, the diabetic model had significantly higher C values of insulin, HOMA-IR, ALT, and GGT, regardless of race, sex, adiposity, and other conventional cardiometabolic risk factor variables ($P < 0.05$).

CONCLUSIONS—The current data links development of prediabetes and type 2 diabetes in apparently healthy adults with concurrent longitudinal changes in the liver function enzyme, along with some cardiometabolic risk variables, since young adulthood. Significant adverse trends of baseline ALT and GGT were noted for both follow-up prediabetic and diabetic groups. Furthermore, there was a significant increased risk

(1.2-fold) of developing type 2 diabetes for elevated ALT and GGT levels (per 1-SD increment) in young adults over a 16-year period, after controlling for alcohol consumption, obesity, and other traditional cardiometabolic risk factors. In terms of predictive value as depicted by the area under the ROC curve analysis, adjusted for relevant covariates, none of the glucose homeostasis variables were significantly better than baseline ALT and GGT in identifying increased risk of follow-up prediabetes and diabetes over an average of a 16-year period.

In the current study, the prevalence of both prediabetes and diabetes was lower than that reported previously (3,17), which could be explained by the lower average age of our cohort. Of note, adiposity, as depicted by BMI, was the strongest predictor of prediabetes and diabetes in this study and in our earlier study (18). As is well known, obesity is pathologically

linked to insulin resistance/hyperinsulinemia and related development of dysglycemia. This is consistent with our earlier studies in that obesity precedes, not follows, hyperinsulinemia/insulin resistance, or metabolic syndrome (19,20). In the current study, the residual effect of these enzymes on the onset of diabetes remained even after controlling for BMI.

The current study, consistent with earlier reports (4,6–9,11), demonstrates an association of ALT and GGT with prediabetes and diabetes. These liver enzymes likely represent the impaired glucose regulation state. The liver is an important site for insulin clearance (8) and production of inflammatory cytokines (8). The adverse association of liver function enzymes to type 2 diabetes may result from the link between excess central (visceral) adiposity, NAFLD, and hepatic insulin resistance mediated by elevated hepatic free fatty acid flux from visceral fat that induces increased hepatic lipogenesis and triglyceride-rich lipoprotein secretion (4,5,21,22). Indeed, an overaccumulation of unoxidized long-chain fatty acids can saturate the storage capacity of adipose tissue, which induces a lipid “spill over” to nonadipose tissue (liver, muscle, heart, and pancreatic β -cells) (23). In such ectopic deposition, excess lipids (hepatic free fatty acids) are driven into an alternate nonoxidative pathway, causing the formation of reactive lipid moieties that evolve into relevant cellular dysfunction and programmed cell death (23). This metabolic disturbance caused by fat infiltration could induce abnormal liver enzyme. Controlling for obesity may not exclude this cellular dysfunction of central deposition of fat.

Moreover, excess central adiposity (and by inference, NAFLD) augments the expression of proinflammatory adipocytokines, including tumor necrosis factor- α , and reduces the expression of insulin-sensitizing and anti-inflammatory adiponectin, which causes an increase in insulin resistance (4,5,24). Insulin resistance, in turn, increases reactive oxygen species and oxidative stress by attenuating the inhibitory effect of insulin on lipid oxidation and by activating CYP2E1, a component of the cytochrome P-450 system (5,25).

Balkau et al. (10) have demonstrated over a 9-year period that fatty liver indices, including liver function enzymes, are simpler clinical tools for predicting diabetes in relatively older adults. In the current long-term longitudinal study, baseline young adult ALT and GGT levels predicted a

Table 3—Discriminatory value of baseline liver function enzymes and glucose homeostasis variables in predicting prediabetes and diabetes: the Bogalusa Heart Study

Variable	C value (95% CI)*	
	Prediabetes	Diabetes
Glucose	0.751 (0.697–0.805)	0.830 (0.777–0.883)
Insulin	0.704 (0.648–0.761)	0.815 (0.761–0.869) ^a
HOMA-IR	0.708 (0.652–0.764)	0.819 (0.765–0.873) ^a
ALT	0.703 (0.648–0.759)	0.814 (0.763–0.866) ^a
GGT	0.701 (0.645–0.757)	0.816 (0.765–0.867) ^a

*C values represent area under the ROC curve, with adjustment for age, race, sex, smoking (yes/no), alcohol drinking (yes/no), BMI, MAP, HDL cholesterol, LDL cholesterol, and triglycerides. ^a $P < 0.05$ vs. prediabetes.

16-year incident type 2 diabetes, even after controlling for alcohol intake, obesity, and other cardiometabolic risk factors.

The current study has certain limitations in that it lacks direct assessments of postchallenge glucose, in vivo insulin action and secretion, body fat mass and distribution, and liver fat content. Instead, we used the simple surrogate measure of glucose homeostasis that is applicable to population studies. Furthermore, information on baseline adipocytokines might have provided additional insight into the development of diabetes.

In summary, elevations in levels of liver function enzymes ALT and GGT relate to incident prediabetes and type 2 diabetes in apparently healthy younger adults. These results underscore the potential utility of ALT and GGT as biomarkers, along with obesity status, in the evaluation of diabetes risk in this age-group.

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