

Liver Enzymes and Incident Diabetes

Findings from the European Prospective Investigation Into Cancer and Nutrition (EPIC)-Potsdam Study

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OBJECTIVE — We sought to examine the association between plasma concentrations of liver enzymes γ -glutamyltransferase (GGT) and alanine transaminase (ALT) and incident diabetes, prospectively.

RESEARCH DESIGN AND METHODS — We conducted a case-cohort analysis of data from participants mainly aged 35–65 years in the European Prospective Investigation into Cancer and Nutrition–Potsdam Study. The analytic sample included 787 participants with incident diabetes and 2,224 participants without diabetes.

RESULTS — Concentrations of GGT and ALT were significantly associated with incident diabetes after extensive adjustment. Compared with participants in the lowest quintile of GGT, the adjusted hazard ratios for increasing quintiles were 1.13 (95% CI 0.66–1.93), 1.67 (1.01–2.77), 2.77 (1.71–4.49), and 2.67 (1.63–4.37), respectively (P for linear trend <0.001). Compared with participants in the lowest quintile of ALT, the adjusted hazard ratios for incident diabetes were 0.93 (0.56–1.53) for quintile 2, 1.28 (0.83–1.96) for quintile 3, 1.35 (0.88–2.07) for quintile 4, and 1.93 (1.27–2.92) for quintile 5 (P for linear trend = 0.002). The magnitude of the associations were higher among men than women for GGT ($P = 0.004$) but did not differ significantly between men and women for ALT ($P = 0.307$).

CONCLUSIONS — Concentrations of GGT and ALT were significant predictors of incident diabetes in this study, even at concentrations still considered to be within the normal range.

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Emerging evidence suggests that a strong link exists between certain liver enzymes such as γ -glutamyltransferase (GGT) (1–13) and alanine transaminase (ALT) (13–16) and diabetes. GGT and the ratio between aspartate aminotransferase and ALT are used as markers of alcohol use. These liver enzymes may be involved in several critical processes that affect the risk of developing conditions such as diabetes and cardiovascular disease. First, GGT and ALT may reflect the accumulation of hepatic fat (17) and, thus, may represent an indirect marker of hepatic insulin resistance

(18). The deposition of fat in the liver leads to an increase in gluconeogenesis and a decrease in the storage of glucose as glycogen in the liver (19). Second, oxidative stress may play a role in the pathogenesis of diabetes (20), and GGT may represent a nonspecific marker of oxidative stress (21). Under conditions of oxidative stress, GGT is induced to help regulate the redox status by breaking down extracellular glutathione to provide cysteine for new intracellular synthesis of glutathione.

Because fatty liver occurs more commonly among men than women and the

distributions of concentrations of GGT and ALT differ between men and women, the possibility exists that the associations between these liver enzymes and incident diabetes may differ by sex. Only a few studies have reported risk estimates separately for men and women (4,8,10,12). Those studies provided no clear pattern as to whether the associations between elevations of concentrations of liver enzymes and incident diabetes differed among men and women. Because some of these studies had a limited number of end points, the CIs around the hazard ratios were wide, precluding any definitive examination of potential sex differences. Therefore, the objectives of this study were twofold: to examine whether the liver enzymes GGT and ALT predicted the onset of diabetes and to determine whether any such associations differed among men and women. To pursue these objectives, we conducted a case-cohort analysis using data from a large prospective German study.

RESEARCH DESIGN AND METHODS

The European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study is part of the multicenter prospective cohort study EPIC. In Potsdam, Germany, 27,548 subjects (16,644 women aged 35–65 years and 10,904 men aged 40–65 years) from the general population were recruited between 1994 and 1998 (22–24). The baseline examination included anthropometric measurements, a personal interview including questions on prevalent diseases, and a questionnaire on sociodemographic and lifestyle characteristics. Potential incident cases of diabetes were identified by follow-up questionnaires, which were administered every 2–3 years. Response rates for each of the three waves of follow-up were $\sim 95\%$. We also considered questionnaires that were part of the ongoing fourth wave of follow-up round and were sent out until 31 January 2005. By 31 August 2005, 90% of them had been returned. Consent was obtained from all participants of the study, and approval was given by the Ethical Committee of the State of Brandenburg, Germany.

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Abbreviations: ALT, alanine transaminase; EPIC, European Prospective Investigation into Cancer and Nutrition; GGT, γ -glutamyltransferase

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Ascertainment of type 2 diabetes

Potentially incident cases of diabetes were those with self-reports of a diabetes diagnosis, diabetes-relevant medication, or dietary treatment due to diabetes. All potentially incident cases were verified by questionnaires mailed to the diagnosing physician asking about the date and type of diagnosis, diagnostic tests, and treatment of diabetes. Only cases with a physician diagnosis of type 2 diabetes (ICD10: E11) and a diagnosis date after the baseline examination were considered as confirmed incident cases of type 2 diabetes. Only these confirmed cases of type 2 diabetes were used in the analysis.

Case-cohort construction

A prospective case-cohort study within the EPIC-Potsdam study was designed. We randomly selected 2,500 individuals from all participants of the EPIC-Potsdam study population for a subcohort of which 2,298 remained after exclusion of participants with prevalent diabetes, without blood samples at baseline, or with missing values for study variables. By randomly selecting a subcohort and using the appropriate statistics for this type of research design, the results are expected to be generalizable to the entire cohort without the need of biomarker measurements in the entire cohort. Of the 849 participants with incident diabetes identified in the full cohort, 787 remained for analyses after similar exclusion criteria. Because the subcohort is representative of the full cohort at baseline, the subcohort included 74 subjects who developed incident type 2 diabetes during follow-up. Of the 787 participants with incident diabetes, 713 were identified in the rest of the total cohort and remained as so called "external" cases for analyses.

Plasma concentrations of GGT and ALT were measured using the ADVIA 1650 chemistry system (Siemens Medical Solutions, Erlangen, Germany). Approximate sex-specific quintiles were derived using values for participants from the subcohort who were included in the analyses.

Covariates

Information on educational attainment, smoking, physical strain at work, physical activity, alcohol use at entry into the study and over a participant's lifetime, and women's reproductive health was assessed with a self-administered questionnaire and a personal interview. In addition, waist circumference, BMI, hypertension, and concentrations of total

cholesterol, HDL cholesterol, C-reactive protein, and glucose were included in our analyses. Anthropometric measurement procedures followed standard protocols under strict quality control. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg or the current use of antihypertensive medication. For participants without a blood pressure measurement, responses to the question about whether they had ever had hypertension were used to assign hypertension status. Concentrations of total cholesterol, HDL cholesterol, C-reactive protein, and glucose were measured using the ADVIA 1650 chemistry system (Siemens Medical Solutions, Erlangen, Germany).

Statistical analysis

Differences in baseline characteristics by baseline diabetes status were tested with Wilcoxon's rank-sum test for continuous variables and the χ^2 test for categorical variables. Tests for trend across quintiles of concentrations of liver enzymes were conducted with linear regression using a robust variance estimator for continuous variables and the Cochran-Armitage test for categorical variables. Cox proportional hazards analysis, using Prentice's pseudo-likelihood approach in the computations, was used to estimate hazard ratios and 95% CIs for quintiles of concentrations of GGT and ALT. The hazard ratio represents a measure of effect relating the hazard (i.e., the probability of experiencing an event in a very small time interval) of one level to that of a reference level for a categorical variable and to a unit change of a continuous variable. Age was used as the primary time-dependent variable in all models: entry time was defined as the subject's age at recruitment and exit time as the date of diagnosis, death, or returns of the last follow-up questionnaire (whichever came first). Analyses were adjusted for baseline information including sex, education (in or no training, vocational training, technical school, technical college, or university degree), smoking (never, past, current < 20 cigarettes/day, current ≥ 20 cigarettes/day), physical strain at work (light, moderate, heavy), sports activity (continuous: hours per week), cycling (continuous: hours per week), alcohol intake (< 0.1 , $0.1-5.0$, $5.1-10.0$, $10.1-20.0$, $20.1-40.0$, and > 40.0 g/day), BMI (continuous: kg/m^2), and waist circumference (continuous: cm), as well as concentrations of C-reactive protein (continuous:

Table 1—Unadjusted baseline characteristics among 2,298 participants from a subcohort: EPIC-Potsdam Study 1994–1998 to 2005

Age (years)	49.5 \pm 8.9
Sports activity (h/week)	1.0 \pm 1.8
Bicycling (h/week)	1.8 \pm 2.9
BMI (kg/m^2)	26.0 \pm 4.2
Waist circumference (cm)	85.4 \pm 12.6
Hypertension	41.4
Total cholesterol (mg/dl)	173.7 \pm 37.6
HDL cholesterol (mg/dl)	47.9 \pm 13.0
C-reactive protein (mg/l)	1.7 \pm 3.1
Glucose (mg/dl)	88.0 \pm 20.4
GGT (units/l)	25.8 \pm 62.5
ALT (units/l)	20.5 \pm 13.8
Women	61.7
University degree	38.3
Heavy or very heavy physical strain at work	6.0
Never smoked	47.4
Alcohol use > 40 g/day	8.9

Data are means \pm SD or percentages.

mg/l), total cholesterol (continuous: mg/dl), HDL cholesterol (continuous: mg/dl), and fasting and nonfasting glucose (continuous: mg/dl). The significance of linear trends across quintiles of concentrations of GGT and ALT was tested by assigning each participant the median value for the quintile and modeling this value as a continuous variable. All analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS— Among the 2,298 participants from the subcohort, the mean and median follow-up times were 7.0 and 6.6 years, respectively. The median time until development of diabetes was 3.7 years, and the mean age at the time that diabetes developed was 60.3 years. Baseline characteristics of the subcohort, which is a random sample of the full cohort, are shown in Table 1. Concentrations of GGT ranged from 0 to 2,183 units/l (men: 0–2,183 units/l, women: 0–263 units/l), and those of ALT ranged from 0 to 241 units/l (men: 0–241 units/l, women: 0–190 units/l). The Spearman correlation coefficient between concentrations of GGT and ALT was 0.62 for all subcohort participants (men: 0.61; women 0.48) (all $P < 0.001$).

At baseline, participants who developed diabetes were significantly older; were more likely to be men; had lower educational achievement; were less likely to have never smoked; were more likely to have consumed > 40 g alcohol per day;

were more likely to experience heavy or very heavy physical strain at work; were less active; had a higher BMI and larger waist circumference; had a higher prevalence of hypertension; had higher concentrations of C-reactive protein, cholesterol, and glucose; and had a lower concentration of HDL cholesterol than those without diabetes.

Across quintiles of concentrations of GGT, positive linear trends were present for age, BMI, and waist circumference, prevalence of hypertension and alcohol use, and concentrations of total cholesterol, C-reactive protein, glucose, and ALT (Table 2). Inverse trends were present for bicycling and the percentages of participants who had a university education and who had never smoked. The patterns of covariates across quintiles of concentrations of ALT were generally similar to those of GGT.

After extensive adjustment for covariates, results from proportional hazards analysis showed that increasing concentrations of GGT were significantly associated with a higher risk for developing diabetes (Table 3). Compared with participants who had a concentration of GGT in the lowest quintile (men ≤ 12 units/l, women ≤ 6 units/l), those who had a concentration of GGT in the highest quintile (men ≥ 47 units/l, women ≥ 21 units/l) at baseline had a hazard ratio of 2.67 (95% CI 1.63–4.37).

We also evaluated the effect of excluding participants who had a concentration of GGT greater than the mean plus 3 SDs (>213 units/l). Among the 2,978 remaining participants, the hazard ratios were 1.13 (95% CI 0.66–1.93), 1.56 (0.94–2.61), 2.84 (1.76–4.60), and 2.61 (1.59–4.28) for quintiles 2–5, respectively (P for linear trend <0.001). Thus, the estimates were very similar to those shown in Table 3. After excluding participants with a baseline fasting plasma glucose ≥ 7.0 mmol/l or a nonfasting plasma glucose ≥ 11.1 mmol/l, the hazard ratios for GGT quintiles 2–5 of model 3 as shown in Table 3 among all participants were 1.32 (0.84–2.08), 1.92 (1.25–2.93), 2.25 (1.49–3.41), and 2.50 (1.64–3.80), respectively (P for linear trend <0.001), and the hazard ratios for ALT quintiles 2–5 were 0.98 (0.66–1.45), 1.23 (0.88–1.72), 1.34 (0.96–1.87), and 1.60 (1.16–2.22), respectively (P for linear trend = 0.001).

Because the associations between concentrations of GGT and incident diabetes differed by sex ($P = 0.004$), we also

Table 2—Unadjusted baseline characteristics among 2,298 participants from the subcohort by quintiles of concentrations of GGT and alanine aminotransferase: EPIC-Potsdam Study 1994–1998 to 2005

	GGT (mean concentration units/l)					Alanine aminotransferase (mean concentration units/l)					P
	Quintile 1 (6.6)	Quintile 2 (10.8)	Quintile 3 (15.8)	Quintile 4 (22.5)	Quintile 5 (70.0)	Quintile 1 (10.3)	Quintile 2 (14.2)	Quintile 3 (16.8)	Quintile 4 (21.8)	Quintile 5 (36.2)	
Age (years)	47.4	49.3	49.6	49.7	51.1	47.9	49.0	49.7	50.0	50.4	<0.001
Sports activity (h/week)	1.2	1.1	1.1	1.0	0.9	1.1	1.2	1.0	0.9	0.9	0.116
Bicycling (h/week)	2.2	1.9	1.7	1.8	1.6	1.9	1.9	2.0	1.7	1.6	0.031
BMI (kg/m ²)	24.2	24.8	25.7	26.6	28.0	24.3	24.8	25.5	26.7	28.0	<0.001
Waist circumference (cm)	80.4	82.3	85.1	86.8	91.1	81.2	82.8	83.6	87.2	91.0	<0.001
Hypertension	25.7	34.6	38.2	47.2	58.0	30.5	35.5	36.0	46.7	55.8	<0.001
Total cholesterol (mg/dl)	153.1	169.3	177.6	177.3	187.0	156.6	169.5	175.2	180.8	183.1	<0.001
HDL cholesterol (mg/dl)	45.8	48.8	48.5	48.0	47.8	46.1	48.3	49.1	48.3	47.3	0.214
C-reactive protein (mg/l)	0.9	1.3	1.6	1.8	2.7	1.5	1.2	1.6	2.0	2.1	<0.001
Glucose (mg/dl)	80.1	86.8	88.2	90.3	92.8	82.9	87.0	87.0	88.2	93.6	<0.001
GGT (units/l)	—	—	—	—	—	12.0	15.2	20.3	24.9	51.3	<0.001
ALT (units/l)	13.7	15.8	19.8	21.1	30.8	—	—	—	—	—	—
Women	59.8	62.0	58.8	65.2	61.8	59.3	56.4	64.9	62.1	63.5	0.065
University degree	41.2	42.5	41.6	36.3	30.7	44.0	42.5	37.3	37.6	32.4	<0.001
Heavy or very heavy physical strain at work	6.6	5.1	6.6	5.3	6.6	5.4	6.8	6.0	7.3	4.8	0.768
Never smoked	51.7	54.3	43.9	44.4	43.9	43.3	47.7	51.4	45.4	48.3	0.316
Alcohol use >40 g/day	5.0	8.1	6.4	8.8	15.4	7.6	9.5	8.2	7.5	11.4	0.134

Data are means or percentages. GGT quintiles for men were defined as ≤ 12 , 13–18, 19–27, 28–46, and ≥ 47 units/l. Quintiles for women were defined as ≤ 6 , 7–9, 10–12, 13–20, and ≥ 21 units/l. ALT quintiles for men were defined as ≤ 15 , 16–19, 20–25, 26–33, and ≥ 34 units/l. Quintiles for women were defined as ≤ 10 , 11–12, 13–15, 16–19, and ≥ 20 units/l.

Table 3—Adjusted hazard ratios (95% CI) for incident diabetes by quintiles of concentrations of GGT and ALT among 3,011 participants: EPIC-Potsdam Study 1994–1998 to 2005

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for linear trend
GGT						
Total						
Model 1	1.00	1.77 (1.10–2.87)	3.12 (1.99–4.89)	6.01 (3.89–9.28)	8.48 (5.52–13.04)	<0.001
Model 2	1.00	1.42 (0.85–2.35)	2.14 (1.34–3.44)	3.60 (2.28–5.68)	4.30 (2.74–6.75)	<0.001
Model 3	1.00	1.13 (0.66–1.93)	1.67 (1.01–2.77)	2.77 (1.71–4.49)	2.67 (1.63–4.37)	<0.001
Men						
Model 1	1.00	1.84 (1.00–3.37)	3.64 (2.07–6.39)	7.37 (4.22–12.87)	7.27 (4.17–12.68)	<0.001
Model 2	1.00	1.29 (0.67–2.50)	2.28 (1.25–4.16)	4.00 (2.20–7.28)	3.49 (1.92–6.36)	<0.001
Model 3	1.00	1.03 (0.52–2.04)	1.81 (0.96–3.41)	3.33 (1.80–6.15)	2.15 (1.13–4.06)	0.035
Women						
Model 1	1.00	1.76 (0.81–3.82)	2.35 (1.11–4.99)	3.95 (1.97–7.93)	9.23 (4.65–18.28)	<0.001
Model 2	1.00	1.46 (0.66–3.21)	1.74 (0.81–3.71)	2.48 (1.24–4.96)	4.37 (2.19–8.73)	<0.001
Model 3	1.00	0.99 (0.45–2.20)	0.99 (0.44–2.25)	1.35 (0.65–2.80)	2.01 (0.96–4.23)	<0.001
ALT						
Total						
Model 1	1.00	1.21 (0.80–1.84)	1.96 (1.36–2.83)	2.61 (1.81–3.76)	5.55 (3.93–7.83)	<0.001
Model 2	1.00	1.25 (0.80–1.94)	1.55 (1.05–2.30)	1.73 (1.17–2.56)	2.93 (2.02–4.25)	<0.001
Model 3	1.00	0.93 (0.56–1.53)	1.28 (0.83–1.96)	1.35 (0.88–2.07)	1.93 (1.27–2.92)	<0.001
Men						
Model 1	1.00	1.36 (0.80–2.29)	2.69 (1.68–4.30)	2.82 (1.73–4.62)	6.49 (4.09–10.30)	<0.001
Model 2	1.00	1.50 (0.84–2.66)	2.23 (1.33–3.75)	1.64 (0.95–2.83)	3.54 (2.10–5.95)	<0.001
Model 3	1.00	1.19 (0.63–2.25)	1.68 (0.94–3.00)	1.28 (0.69–2.35)	2.19 (1.24–3.88)	0.048
Women						
Model 1	1.00	0.99 (0.49–2.00)	1.14 (0.64–2.02)	2.18 (1.25–3.79)	4.40 (2.62–7.40)	<0.001
Model 2	1.00	1.12 (0.53–2.37)	0.96 (0.50–1.83)	1.71 (0.94–3.13)	2.22 (1.26–3.93)	<0.001
Model 3	1.00	1.05 (0.46–2.42)	1.02 (0.53–1.96)	1.42 (0.77–2.64)	1.54 (0.85–2.78)	0.048

Model 1: Adjusted for age, sex, educational status, smoking status, alcohol use, occupational activity, and sports activity. Model 2: Adjusted for age, sex, educational status, smoking status, alcohol use, occupational activity, sports activity, waist circumference, and BMI. Model 3: Adjusted for age, sex, educational status, smoking status, alcohol use, occupational activity, sports activity, waist circumference, BMI, systolic blood pressure, and concentrations of total cholesterol, HDL cholesterol, C-reactive protein, and glucose. GGT quintiles for men were defined as ≤ 12 , 13–18, 19–27, 28–46, and ≥ 47 units/l. Quintiles for women were defined as ≤ 6 , 7–9, 10–12, 13–20, and ≥ 21 units/l. ALT quintiles for men were defined as ≤ 15 , 16–19, 20–25, 26–33, and ≥ 34 units/l. Quintiles for women were defined as ≤ 10 , 11–12, 13–15, 16–19, and ≥ 20 units/l.

calculated hazard ratios for men and women separately. The hazard ratios were larger in men than women (Table 3).

In addition, participants with a concentration of ALT in the highest quintile (men ≥ 34 units/l, women ≥ 20 units/l) had a hazard ratio of 1.93 (95% CI 1.27–2.92) compared with those who had a concentration in the lowest quintile (men ≤ 15 units/l, women ≤ 10 units/l). The association between concentrations of ALT and incident diabetes was similar between men and women (P for interaction between sex and ALT = 0.307).

Finally, we examined whether the association between concentrations of liver enzymes and incident diabetes varied according to menopausal status by modeling the interaction between liver enzymes (as continuous variables) and menopausal status. These analyses were limited to 1,187 women for whom a determination about menopausal status was possible (196 had incident diabetes). For

neither GGT ($P = 0.863$) nor ALT ($P = 0.348$) was there evidence of effect modification by menopausal status.

CONCLUSIONS— The results from the EPIC-Potsdam study with a large number of incident cases of diabetes support previous findings that described significant associations between liver enzymes, especially GGT and ALT, and diabetes incidence. The association between concentrations of GGT and incident diabetes was stronger among men than women. Of note is that a substantial and significant increase in the hazard ratios occurred at concentrations of liver enzymes thought to be in the normal range, particularly among men. One medical reference places the upper limit of the normal range of GGT at 30 units/l for men and 24 units/l for women and that of ALT at 40 units/l for men and 35 units/l for women (25).

Although interest in liver enzymes in

patients with diabetes goes back at least several decades, prospective studies examining the relationships between concentrations of liver enzymes and incident diabetes have been conducted mostly since the late 1990s. GGT appears to have been included in the largest number of prospective studies, followed by ALT, aspartate aminotransferase, and alkaline phosphatase.

Most of the previous studies that examined the associations between concentrations of GGT (1–13) or ALT (2,3,6,13–16) and incident diabetes reported a positive association. The findings from our study are consistent with those studies. However, the few previous studies that examined sex-specific associations between concentrations of liver enzymes and incidence of diabetes produced inconsistent results. In two of these studies, the hazard ratios in men exceeded those in women (10,12); in one study, the hazard ratio in women exceeded that in men

(8); and in one study, the results were mixed (4). The results from our investigation of GGT showed higher hazard ratios among men than women. Among men, the risk for developing diabetes increased rapidly up to concentrations of ~25 units/l, whereas among women, the risk increased more progressively over the range of concentrations of GGT.

Several limitations deserve comment. First, incident diabetes was obtained from self-reported information confirmed by the participants' physicians. Thus, some proportion of total diabetes was not identified. If, however, the association between concentrations of the liver enzymes and incident undiagnosed diabetes were of the same magnitude as those for incident diagnosed diabetes, the hazard ratios in our study should not have been biased. Second, a measure of insulin resistance was not available. It is conceivable that the hazard ratios would have been attenuated to some degree had such measures been available. However, other studies that were able to adjust for true or surrogate measures of insulin resistance still reported significant associations between raised concentrations of liver enzymes and incident diabetes (2,7,12). Third, despite adjusting the results for a substantial number of potential confounders, we may not have included all relevant confounders. In addition, the results are subject to residual confounding. Fourth, information to eliminate participants with various sources of liver pathology such as viral hepatitis was not available. It is unclear how this may have affected our results, but our sensitivity analysis in which we excluded participants with a concentration of a liver enzyme more than the mean plus 3 SDs suggests that the results would not have been materially affected. Fifth, only a single measurement of concentration of liver enzymes was made. If regression dilution bias played a role, it is possible that our results underestimated the strength of the associations.

Concentrations of liver enzymes are routinely measured as part of clinical chemistry panels and, thus, are readily available for many people. Because an accumulating body of evidence during the past decade suggests that elevations of GGT and ALT are associated with an increased risk of diabetes and because the reported magnitude of these associations is considerable, thought needs to be given to how values of these enzymes can be incorporated into clinical practice to help identify people who are at potentially in-

creased risk for developing diabetes and who may benefit from more intensive monitoring and perhaps treatment with behavioral interventions (such as weight loss) or medications. Complicating matters somewhat is that risk is already increased at concentrations that are still thought to be within the normal range. Thus, revision of what is now considered to reflect normal concentrations of liver enzymes may be warranted (26).

In conclusion, elevations of concentrations of GGT and ALT translated into an increase in the incidence of diabetes in this prospective study over a median period of 6.5 years. Although the mechanisms for these associations along with possible avenues of interventions require further investigation, the considerable knowledge base at present seriously merits considering elevations of GGT and possibly those of ALT as pointing to an increased potential for developing diabetes.

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