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Liver enzymes and risk of diabetes and cardiovascular disease: Results of the Firenze Bagno a Ripoli (FIBAR) study

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Abstract

The aim of the study was to assess γ-glutamyl transpeptidase (γ-GT), alanine aminotransferase, and aspartate aminotransferase (AST) in the prediction of diabetes and cardiovascular disease (CVD) in subjects free from hepatic diseases other than nonalcoholic fatty liver disease. The present analysis was performed on the cohort of subjects enrolled in the Firenze Bagno a Ripoli (FIBAR) study, a screening program for diabetes performed between 1 March 2001 and 31 December 2003 in the city of Florence on 3124 subjects who underwent an oral glucose tolerance test. Incident cases of diabetes in nondiabetic subjects (n = 2662) were obtained through databases of drug prescriptions, hospital admissions, and lists of subjects eligible for reimbursement. Incident CVD in subjects free of diabetes and CVD at enrollment (n = 2617) was identified through hospital admissions and through the register of causes of death. Mean follow-up was 39.6 ± 12.0 months and 39.8 ± 11.4 months for diabetes and CVD, respectively. Yearly incidence of diabetes and CVD was 0.4% and 0.2%, respectively. After adjustment for age and sex, γ-GT >40 U/L was associated with increased incidence of diabetes and CVD (hazard ratio [95% confidence interval]: 2.54 [1.26-5.11], $P < .05$ and 2.21 [0.98-5.43], $P < .10$, respectively). Risk of diabetes, but not of CVD, was increased in patients with γ-GT in the 25- to 40-U/L range. After adjustment for confounders, AST >40 U/L predicted CVD (hazard ratio, 6.5 [95% confidence interval, 1.5-28.1]), but not diabetes. Elevated γ-GT or AST is an independent predictor of CVD. An increase of γ-GT levels above the reference range, or also in the upper reference range, is an independent predictor of incident diabetes.

1. Background

Elevation of liver enzymes has been reported to be associated with increased risk for diabetes [1-13] and cardiovascular disease [14-16]. In particular, a greater incidence of diabetes has been reported in patients with higher γ-glutamyl transferase (γ-GT) levels [1-3,6-10,12,13]. Alanine aminotransferase (ALT) is also associated with incident diabetes [3,9,11-13,17,18], although to a lesser extent than γ-GT [3,9,12], whereas aspartate aminotransferase (AST) levels have been reported to be only marginally predictive of incident diabetes [3,9,13,17]. Conversely, higher levels of both ALT [15,19] and γ-GT [14,16,19] have been reported to be similarly associated with increased cardiovascular morbidity and mortality.

The aim of this prospective cohort study is the comparison of γ-GT, ALT, and AST in the prediction of diabetes and cardiovascular disease in subjects free from hepatic diseases other than nonalcoholic fatty liver disease (NAFLD).

2. Patient and methods

The present analysis was performed on the cohort of subjects enrolled in the Firenze Bagno a Ripoli (FIBAR) study, a screening program for diabetes performed between 1 March 2001 and 31 December 2003 in the

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city of Florence and in the nearby town of Bagno a Ripoli, which was described elsewhere in greater detail [20]. Briefly, all subjects aged 40 to 75 years without known diabetes were invited to participate through newspaper and television advertising and public conferences; furthermore, 6721 letters were sent from a group of family physicians collaborating with the project to all eligible subjects among their registered patients. The local ethical committee approved the study, and each participant provided informed written consent. Of the 3124 individuals who accepted to participate, 1704 had been invited through personal letters (which therefore had a response rate of 25.3%), whereas the others had been informed through newspaper and television advertising and public conferences, or by friends or relatives.

Venous blood samples for lipid profile and plasma glucose were collected in the morning after overnight fast (>8 hours). All subjects underwent a standard oral glucose tolerance test (75 g in 50% water solution, with measurement of plasma glucose after 120 minutes). A detailed personal and medical history was collected, including current and previous relevant medical conditions and any current pharmacological treatment. Weight, height, and waist circumference were measured following the World Health Organization recommendations [21]. Blood pressure was measured in sitting position after a 5-minute rest using a mercury sphygmomanometer with a cuff of appropriate size; the mean of 3 measurements of systolic and diastolic blood pressure was considered for analysis. Laboratory determinations were performed in the Central Laboratory of Careggi Hospital in Florence. Plasma glucose was measured by a glucose oxidase method; total and high-density lipoprotein (HDL) cholesterol, triglycerides, ALT, AST, and γ-GT were determined by an automated enzymatic method (Aeroset, Abbott Laboratories (Milan, Italy); ALT and AST with a nicotinamide adenine dinucleotide (NADH) oxidation, and γ-GT with a L-γ-glutamyl-3-carboxy-4-nitroanilide substrate). The assay is linear up to 942, 913, and 1543 U/L for ALT, AST, and γ-GT, respectively, with a limit of quantitation of 5.1, 2.2, and 3.3 U/L, respectively. The intra- and interassay reliability is greater than 94.7%, 95.3%, and 95.1%, for ALT, AST, and γ-GT, respectively.

Diagnosis of diabetes mellitus at enrollment was made according to the American Diabetes Association criteria [22], and metabolic syndrome was diagnosed according to the National Cholesterol Education Program (NCEP) [23] and the International Diabetes Federation (IDF) [24] criteria. Hypertension was defined according to the World Health Organization criteria [21]; for hypertriglyceridemia and low HDL cholesterol, thresholds proposed by NCEP [23] for the definition of metabolic syndrome were used. Alanine aminotransferase, AST, and γ-GT were considered increased when above the upper limit of the reference range of the laboratory (40 U/L for all the three).

2.1. Incident diabetes

Of the 3124 subjects studied, 165 showed a fasting glucose >7.0 mmol/L and/or a 2-hour postload glucose >11 mmol/L and were therefore excluded from the analysis. Furthermore, patients with the following conditions (n = 297) were excluded: known liver disease other than NAFLD (hepatitis, cirrhosis, malignancies, etc); metastatic cancer; severe heart failure (New York Heart Association class III or IV); recent cholelithiasis (<1 month); self-reported alcohol consumption of more than 2 drinks a day; and chronic treatment (<1 month) with potentially hepatotoxic medications, including acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids.

Follow-up of each subject (n = 2662) was continued until diagnosis of diabetes, death, or until 31 December 2005. Mean follow-up was 39.6 ± 12.0 months.

Newly diagnosed cases of diabetes within 31 December 2005 were identified from 3 different sources:

1. Register of diabetic patients in Florence Local Unit of the National Health Service. All diabetic patients are encouraged to register to obtain full reimbursement for diabetes-related drugs, medical devices (ie, insulin syringes, glucose self-monitoring equipment, etc), laboratory tests, diagnostic procedures, and medical visits. To obtain registration, patients need a certification by their family physicians or by an endocrinologist or diabetes specialist.
2. Reimbursement for use of oral hypoglycemic drugs and/or insulin.
3. Hospital admissions, with diabetes (*International Classification of Diseases* [ICD] code 250) included among diagnoses at discharge. Cases were identified through the Tuscany Regional Hospital Discharge System database.

This register-based identification of newly diagnosed cases of diabetes has the advantage of avoiding losses at follow-up. In fact, diabetes status can be assessed in all subjects until death, change of residence, or planned end of follow-up. No systematic screening of diabetes (either through fasting glucose or oral glucose tolerance test) was performed during follow-up.

2.2. Incident cardiovascular events

After the exclusion of further 45 patients with previously known cardiovascular disease, the follow-up of the remaining 2617 subjects was continued until diagnosis of major cardiovascular events (determining death or requiring hospitalization), death, or until 31 December 2005. Mean follow-up was 39.8 ± 11.4 months.

Diagnoses of cardiovascular events (including fatal events) were obtained through ICD-9 codes: 410 to 414 (ischemic heart disease), 420 to 429 (other heart diseases), and 798 to 799 (sudden death) for cardiac disease; 430 to 434

Table 1
Characteristics of the sample for incident diabetes

Baseline parameters	Diabetes at follow-up		
	No (n = 2626)	Yes (n = 36)	*P* (95% CI)
Sex (%, female)	57.2	47.8	NS
Age (y)	54.2 ± 11.3	63.7 ± 7.7	<.05
BMI (kg/m^2)	25.9 ± 4.0	29.3 ± 4.9	<.01
Total cholesterol (mg/dL)	207.4 ± 37.4	211.2 ± 35.8	NS
AST (IU/L)	19 (16-23)	21 (18-23)	<.05
ALT (IU/L)	19 (14-26)	28 (19-38)	<.001
γ-GT (IU/L)	22 (16-33)	33 (22-58)	<.001
Impaired glucose tolerance (%)	9.0	55.6	<.001
Metabolic syndrome (%, NCEP)	13.0	66.7	<.001
Metabolic syndrome (%, IDF)	24.5	77.8	<.001
Hypertension (%)	44.5	77.8	<.001
Hypertriglyceridemia (%)	19.5	44.4	<.01
Low HDL cholesterol (%)	12.9	33.3	<.01
High waist (%, NCEP)	28.5	63.9	<.01
High waist (%, IDF)	61.5	91.7	<.01
High fasting PG (%, NCEP)	10.7	100	<.001
High fasting PG (%, IDF)	31.3	100	<.01

Data are expressed as mean ± SD, median (quartiles), or prevalence (%). Impaired glucose tolerance: postload glucose, 7.8 to 11 mmol/L. Hypertension: systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or antihypertensive treatment. Hypertriglyceridemia: triglyceride ≥1.7 mmol/L and/or drug treatment. Low HDL cholesterol: <1.04 mmol/L for men and <1.30 mmol/L for women [23]. PG indicates plasma glucose.

and 436 to 438 for cerebrovascular disease; and 36 to 40 for revascularization (angioplasty/bypass).

2.3. Statistical analyses

Statistical analysis was performed on SPSS 12.0.1 (SPSS, Chicago, IL). Data were expressed as mean ± SD when normally distributed and as median (quartiles) when their distribution was not normal (as in the case of ALT, AST, and γ-GT). For comparisons between groups, unpaired 2-tailed Student *t* tests and Mann-Whitney *U* tests were applied to normally and non-normally distributed parameters, respectively. The χ^2 test was used for between-group comparisons of categorical variables. Kaplan-Meier analysis was carried out to assess differences in incidence of diabetes between groups. Relative risk of diabetes (with 95% confidence interval [CI]) was calculated in different groups. A stepwise Cox regression was performed for the assessment of the association of liver enzyme levels (used as continuous variables and reported as hazard ratios [HRs] for each 10-U/L increment) with incident diabetes and cardiovascular disease after adjusting for confounders. Alternative models, with different confounders included (model 1: age and sex; model 2: age, sex, alcohol [reported no. of drinks], smoking status, and metabolic syndrome; model 3: age, sex, alcohol [reported no. of drinks], smoking status, and fasting plasma glucose), were tested separately for each liver enzyme; only HRs for liver enzymes were reported. Receiver operating characteristic (ROC) curve analysis was used to identify a possible threshold of γ-GT capable of detecting at least two thirds of incident cases of diabetes.

3. Results

Among subjects enrolled, 15 died within the period of observation. Furthermore, 36 new cases of diabetes were recorded, with a yearly incidence rate of 0.4%. Characteristics of individuals who developed diabetes are summarized in Table 1. Incident diabetes was associated with higher age, adiposity, and fasting glucose and with a higher prevalence of hypertension, hypertriglyceridemia, and low HDL cholesterol. Furthermore, higher AST, ALT, and γ-GT levels were observed in subjects who developed diabetes during follow-up.

Elevated (>40 U/L) γ-GT, ALT, or AST was observed in 15.8%, 7.3%, and 1.7% of enrolled subjects, respectively. Individuals with γ-GT >40 U/L showed a significantly greater incidence of diabetes. A similar increase in diabetes incidence was observed in those with elevated (>40 U/L) ALT or AST (Fig. 1). Similar results were obtained when patients with enzyme levels above 3 times the upper limit

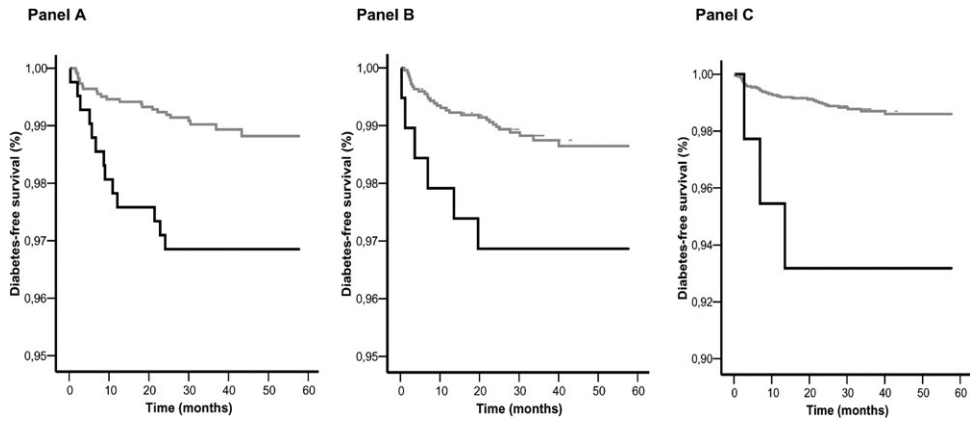

Fig. 1. Proportion of subjects free from incident diabetes among those with normal and elevated (>40 U/L) γ-GT (A), ALT (B), and AST (C) levels; all $P < .01$.

of the reference range were excluded from the analysis (data not shown).

At multivariate analysis, all 3 parameters were associated with incidence of diabetes after adjustment for age and sex. The association of liver enzymes with incident diabetes retained statistical significance even after adjustment for multiple confounders, including metabolic syndrome; conversely, only γ-GT was a significant predictor of diabetes when adjusted for fasting glucose (Table 2).

Subjects in the upper quartile of γ-GT (>33 U/L) showed a significantly ($P < .05$) higher incidence of diabetes than those in the second and third quartiles, who, in turn, had a higher incidence than individuals in the lower quartile (<16 U/L). The ROC curve analysis suggested that a threshold of γ-GT at 25 U/L could identify 67% of cases of incident diabetes, with a specificity of 57%. The unadjusted odds ratio (OR) for diabetes associated with γGT >40, 33, and 25 U/L was 3.07 (1.56-6.06), 2.92 (1.52-5.62), and 2.64 (1.32-5.28), respectively (all $P < .01$). After adjustment for age and sex, the HR for diabetes associated with elevated γ-GT was 2.54 (1.26-5.11), 2.43 (1.23-4.78), and 2.20 (1.06-4.53) for thresholds at 40, 33, and 25 U/L, respectively.

After the exclusion of patients with previously known cardiovascular disease, 20 of the remaining 2617 subjects (Table 3) showed major cardiovascular events (determining death or requiring hospitalization) during follow-up (mean, 39.8 ± 11.4 months), with a yearly incidence rate of 0.2%. Incident cardiovascular events were associated with higher age and total cholesterol and with higher prevalence of hypertension. Furthermore, higher γ-GT levels were observed in subjects who developed cardiovascular events during follow-up.

Elevated (>40 U/L) γ-GT and AST, but not ALT, were significantly associated with a higher incidence of cardiovascular disease during follow-up (unadjusted OR [95% CI]: 3.31 [1.32-8.13], $P = .009$; 6.24 [1.44-26.71], $P = .014$; and 0.70 [0.10-5.12], $P = .716$, respectively). After adjustment for age and sex, HR (95% CI) for incident cardiovascular disease of elevated γ-GT, AST, and ALT was 2.21 (0.98-5.43) ($P = .09$), 6.52 (1.51-28.12) ($P = .025$), and 0.73 (0.12-5.63) ($P = .763$). Elevation of γ-GT over the previously defined thresholds of 33 and 25 U/L was not associated with a significantly increased risk of cardiovascular disease (unadjusted OR: 3.68 [1.33-10.22] and 2.58 [1.05-6.35]; age- and sex-adjusted HR: 1.44 [0.61-3.52] and 1.71 [0.68-4.67], respectively).

Table 2
Risk of incident diabetes as a function of liver enzyme levels

	HR (95.0% CI)		*P*	
	Diabetes	CV events	Diabetes	CV
Model 1				
AST	1.553 (1.137-2.123)	1.505 (1.070-2.409	.006	.045
ALT	1.389 (1.261-1.530)	1.006 (0.637-1.462)	<.001	.826
γ-GT	1.086 (1.048-1.124)	1.089 (1.041-1.140)	<.001	<.001
Model 2				
AST	1.494 (1.061-2.104)	1.566 (1.059-2.512)	.021	.038
ALT	1.304 (1.171-1.451)	1.015 (0.673-1.530)	<.001	.944
γ-GT	1.091 (1.037-1.146)	1.092 (1.043-1.144)	.001	<.001
Model 3				
AST	0.990 (0.722-1.356)	1.565 (1.021-2.442)	.948	.042
ALT	1.012 (0.905-1.132)	1.006 (0.672-1.515)	.835	.939
γ-GT	1.073 (1.021-1.128)	1.095 (1.043-1.150)	.006	<.001

Data are provided as HR for each 10-U/L increment. *P for diabetes; **P for cardiovascular events. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, alcohol (reported no. of drinks), smoking status, and metabolic syndrome. Model 3: adjusted for age, sex, alcohol (reported no. of drinks), smoking status, and fasting plasma glucose. CV indicates cardiovascular.

Table 3
Characteristics of the sample for incident cardiovascular events

Baseline parameters	CV events at follow-up		
	No (n = 2597)	Yes (n = 20)	*P*
Sex (%, female)	58.3	75.0	.001
Age (y)	54.5 ± 11.5	63.1 ± 9.2	.001
BMI (kg/m^2)	25.8 ± 4.2	26.3 ± 3.7	NS
Total cholesterol (mg/dL)	207.6 ± 37.1	226.4 ± 52.1	<.05
AST (IU/L)	19 (16-23)	21 (16-27)	NS
ALT (IU/L)	19 (14-26)	20 (15-31)	NS
γ-GT (IU/L)	22 (16-33)	29 (21-49)	<.01
Impaired glucose tolerance (%)	9.7	15.0	NS
Metabolic syndrome (%, NCEP)	14.2	15.0	NS
Metabolic syndrome (%, IDF)	25.7	35.0	NS
Hypertension (%)	44.2	80.0	<.01
Hypertriglyceridemia (%)	19.6	30.0	NS
Low HDL cholesterol (%)	13.2	15.0	NS
High waist (%, NCEP)	28.7	35.0	NS
High waist (%, IDF)	61.9	60.0	NS
High fasting PG (%, NCEP)	10.7	15.0	NS
High fasting PG (%, IDF)	33.2	40.0	NS

Data are expressed as mean ± SD or prevalence (%). NS indicates not significant; CV, cardiovascular; NCEP, National Cholesterol Education Program; IDF, International Diabetes Federation; PG, postprandial glycemia.

4. Discussion

The present results confirm that elevated γ-GT levels are associated with increased incidence of diabetes [1-3,6-10,12]. Notably, even γ-GT in the upper reference range (>16-20 U/L) is predictive of incident diabetes, as previously described [1-3,6,8,9,12]. In fact, in the present sample, a threshold of 25 U/L for γ-GT is not inferior to 33 U/L (upper quartile) or 40 U/L (conventional upper limit of reference range) in the prediction of incident diabetes. It is also possible that different thresholds could be used in women and men; however, the limited size of the present sample did not allow a reliable analysis for each sex.

In comparison with ALT or AST, γ-GT has a lower specificity as a marker of liver damage. Despite this fact, γ-GT is more predictive of diabetes than the other liver enzymes. It can be speculated that multiple drug treatments, increasing the risk of diabetes, may have determined an alteration of γ-GT, rather than ALT or AST, in some cases. Alternatively, the increase of γ-GT could have a greater

association with insulin resistance and related metabolic abnormalities in comparison with other liver enzymes.

Elevated γ-GT has been reported to be associated with a greater morbidity [25-27] and mortality [14] for cerebrovascular disease, although its relationship with coronary artery disease is controversial [14,26]. In our sample, γ-GT levels above the reference range predicted cardiovascular disease, whereas levels in the upper reference range did not appear to be associated with increased cardiovascular risk. Although the limited size of the sample does not allow the drawing of definitive conclusions on this point, it could be speculated that γ-GT levels could have different thresholds when used as markers of risk of diabetes or of cardiovascular disease. On the other hand, the size of the present sample could have been insufficient to detect an association between γ-GT in the upper reference range and incident cardiovascular disease.

Although ALT is a recognized marker of risk for diabetes [3,9,11,12,17], elevation of γ-GT is reported to be superior to ALT in the prediction of incident diabetes [3,9,12]. In our sample, both γ-GT and ALT were similarly predictive of diabetes at Kaplan-Meier and ROC curve analysis. At multivariate analysis, only γ-GT retained statistical significance after adjustment for metabolic syndrome; however, this could be due to the fact that a lower proportion of subjects showed elevated ALT, in comparison with increased γ-GT. In fact, although less frequent, the increase of ALT seems to be similarly predictive of diabetes as the increase of γ-GT. On the other hand, ALT was not predictive of cardiovascular disease, in contrast with previous observations [15]; but this could be due to the insufficient size of the sample. In fact, the sample size is adequate for adjustments for up to 2 (as in model 1 of Table 2) or 3 confounders for cardiovascular events and diabetes, respectively; results obtained with more complex models (such as models 2 and 3) should therefore be considered with great caution.

Nonalcoholic fatty liver disease, which is characterized by elevated hepatic triglyceride content, is associated with insulin resistance [28] and increased risk for diabetes [2,9,11,12,17] and cardiovascular disease [29,30]. This condition, which is frequent in overweight and obese subjects [31], is often associated with an increase of circulating liver enzymes and, in particular, of γ-GT [32] and ALT [33]. Increased γ-GT and ALT cannot be considered a reliable marker of NAFLD because of the many cases of fatty liver with normal enzyme levels [34]. However, patients with NAFLD show, on average, higher enzyme levels than the rest of general population; it is therefore plausible that the observed association of higher γ-GT and ALT with incident diabetes and cardiovascular disease is due to a greater prevalence of NAFLD in patients with elevated liver enzymes.

Increase of AST has been reported to be moderately predictive of incident diabetes, although to a lesser extent in comparison with elevated γ-GT and/or ALT [2,3,9,17]. Conversely, the predictive value of higher AST for cardiovascular disease has not been reported to date. In the present cohort, the association of higher AST with incident diabetes was weaker than that of γ-GT and ALT, confirming previous reports [2,3,9,17]. On the other hand, AST levels above the reference range were associated with a relevant increase of the incidence of cardiovascular disease. Increase of AST, although less frequent in this population, appeared to be a stronger predictor of cardiovascular disease than that of ALT and γ-GT. The mechanisms underlying this association of higher AST with cardiovascular disease are difficult to identify. Increase of AST is associated with insulin resistance [35], which is a relevant cardiovascular risk factor; however, the implication of other, still unknown mechanisms cannot be excluded.

It should be considered that the sample enrolled in the FIBAR study is by no means representative of the general population; in fact, subjects participating in a screening program for diabetes have a greater chance of being affected by risk factors for diabetes, such as family history, previous hyperglycemia, or concurrent metabolic abnormalities. As a consequence, increased liver enzymes, as well as risk factors for cardiovascular diseases, could be overrepresented in the sample. However, the observed incidence of diabetes was similar to that expected for an Italian population in the same age range [36].

Another limitation is represented by the fact that no systematic screening of diabetes was performed during follow-up, so that many incident cases could have remained unnoticed. It is conceivable that a higher proportion of subjects with any abnormality in baseline laboratory parameters underwent blood tests during follow-up. As a consequence, the risk associated with elevated liver enzymes could have been overestimated. On the other hand, the use of a validated [37,38], register-based, capture-recapture method allows a reliable estimation of incident diabetes without loss at follow-up. It should also be recognized that previous hepatic disease was excluded only on the basis of medical history; therefore, in some subjects, the elevation of liver enzymes could have been determined by a previously undiagnosed liver disease other than NAFLD.

Elevated liver enzymes could be used as markers of risk for diabetes in clinical settings. In this respect, γ-GT could be superior to either ALT or AST. Notably, γ-GT levels in the upper reference range appear to be already associated with increased diabetes risk. It should be recognized that, even when choosing the most convenient threshold, elevated γ-GT does not show a sufficient predictive value to be used as a straightforward screening test for diabetes; however, the same is true for all known predictors of type 2 diabetes mellitus.

In conclusion, elevation of hepatic enzymes is associated with increased risk of diabetes and cardiovascular disease. Although further studies on larger samples are needed to clarify this point, the circulating liver enzyme profile associated with diabetes risk could be different from that predicting cardiovascular disease.

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