Abnormal Liver Function Test Predicts Type 2 Diabetes

A community-based prospective study

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Increased activities of liver enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltranspeptidase (GGT) are indicators of hepatocellular injury. Increased activity of these markers is associated with insulin resistance (1), metabolic syndrome, and type 2 diabetes (2–9). However, most of these studies were performed in Western countries (2–5,7,9), and the two studies from Japan and Korea were not community based (6,8). In this prospective community-based study, we evaluated the relationships between markers of liver function and the onset of type 2 diabetes after adjusting for potential risk factors including inflammatory markers.

RESEARCH DESIGN AND METHODS — In 2001, the Korean government funded a large community-based epidemiological survey to investigate the trends in diabetes and the associated risk factors (10). For this study, two communities, one from a rural Ansung and the other from an urban Ansan community, were selected. The baseline examination was performed in 2001–2002, and biennial follow-up examinations will continue through 2010. The age range for eligibility was 40–69 years. Of the 7,192 eligible individuals in Ansung, 5,018 were surveyed (70% response rate) using a cluster sampling method. A total of 15,580 individuals were eligible in Ansan, and we successfully recruited 5,020 (32.4%) using a random sampling method of the local telephone directory. The study protocol was approved by the ethics committee of the Korean Health and Genome Study.

Anthropometric parameters and blood pressure were measured by standard methods. Fasting plasma glucose, lipid profiles, insulin, high-sensitivity C-reactive protein, and the activities of hepatic enzymes were measured in a central laboratory.

All participants except those on oral hypoglycemic medications or insulin therapy underwent a 2-h 75-g oral glucose tolerance test at baseline and at each follow-up visit. Pancreatic β-cell function and insulin resistance were calculated using the homeostasis model assessment (HOMA-β and HOMA-IR, respectively) and quantitative insulin sensitivity check index (QUICKI) (11,12).

All data are presented as means ± SD. Statistical analyses were conducted using *t* tests, Pearson's correlation, and logistic regression models by using SPSS (version 12.0; SPSS, Chicago, IL). $P < 0.05$ was considered significant.

RESULTS — At baseline, 594 (5.9%) of 10,038 participants were being treated for diabetes and 542 (5.4%) were newly diagnosed with type 2 diabetes by oral glucose tolerance testing. The clinical and biochemical features of men (n = 4,075) and women (n = 4,675) were investigated after excluding those with a known history of diabetes and those positive for hepatitis B or C by antibody testing. Mean ± SD age was 51.4 ± 8.7 and 52.1 ± 8.9 years in men and women, respectively. Regarding alcohol drinking, the proportion of current drinkers in men was much higher than that in women (71.0 vs. 26.5%, $P < 0.01$). Mean levels of liver enzyme activities were higher in men than those in women (30.8 ± 20.1 vs. 25.3 ± 13.1 IU/l in AST, 31.0 ± 24.8 vs. 21.4 ± 16.0 IU/l in ALT, and 50.4 ± 30.7 vs. 18.8 ± 20.4 IU/l in GGT, respectively; all $P < 0.05$).

Of the three liver enzymes, ALT activity correlated better with BMI than AST or GGT (r = 0.203 vs. r = 0.023 or r = 0.016 in men; r = 0.174 vs. r = 0.058 or r = 0.126 in women, respectively). In the correlation with HOMA-IR, ALT showed a stronger relationship than either AST or GGT (r = 0.104 vs. r = 0.044 or r = 0.025 in men; r = 0.082 vs. r = 0.061 or r = 0.074 in women). When divided into drinkers and nondrinkers, a similar pattern was found in both sexes. Accordingly, ALT was used as the marker for liver function in all subsequent analyses.

We stratified participants into quartiles according to ALT activity in each sex. In the percentage of participants who had obesity, bad lipid profiles, and high glucose, insulin and HOMA-IR increased progressively with ALT quartile in both sexes (Table 1). In contrast, increasing quartiles of ALT were associated with declining QUICKI, HOMA-β, and HDL cholesterol concentration after adjusting for age and alcohol status. The percentage of alcohol drinkers increased with ALT only in men.

At the 2-year follow-up, we found that the highest quartile of ALT level was a predictor of the incidence of type 2 diabetes in both sexes (Table 1). We also found similar results when GGT was used, although the relative risk was lower

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Received for publication 17 January 2007 and accepted in revised form 4 July 2007.

Published ahead of print at http://care.diabetesjournals.org on 12 July 2007. DOI: 10.2337/dc07-0106.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltranspeptidase; HOMA-β, homeostasis model assessment of pancreatic β-cell function; HOMA-IR, homeostastis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical and biochemical characteristics of male and female participants, stratified by ALT quartiles, and relative risk (RR) of ALT quartiles in logistic regression models for incidence of diabetes*

	ALT quartiles (IU/l) in male subjects					ALT quartiles (IU/l) in female subjects				
	1st (<19.0)	2nd (19.3–25.0)	3rd (25.7–35.0)	4th (>35.2)	*P*	1st (< 14.0)	2nd (15.0–18.0)	3rd (18.2–23.5)	4th (>24.0)	*P*
n	1,010	1,025	1,024	1,016		1,133	1,139	1,270	1,133	
Age (years)	53.2 ± 9.1	52.3 ± 9.0	50.9 ± 8.4	49.3 ± 7.8	<0.01	49.8 ± 8.8	51.7 ± 9.0	53.5 ± 9.0	53.3 ± 8.5	<0.01
BMI (kg/m^2)	22.9 ± 2.7	23.8 ± 2.6	24.6 ± 2.8	25.2 ± 3.0	<0.01	23.7 ± 2.9	24.4 ± 3.0	24.9 ± 3.2	25.9 ± 3.4	<0.01
Waist-to-hip ratio	87.6 ± 6.2	89.0 ± 5.8	89.8 ± 5.9	90.8 ± 5.5	<0.01	84.4 ± 8.7	86.3 ± 8.3	87.9 ± 8.2	88.4 ± 8.4	<0.01
Waist (cm)	79.9 ± 7.3	82.6 ± 7.2	84.6 ± 7.3	86.2 ± 7.2	<0.01	77.9 ± 9.1	80.2 ± 9.1	82.3 ± 9.3	84.2 ± 9.6	<0.01
Body fat (%)	19.3 ± 5.1	20.8 ± 5.0	22.1 ± 4.9	23.1 ± 4.9	<0.01	29.6 ± 5.3	30.9 ± 5.4	31.8 ± 5.3	33.2 ± 5.2	<0.01
hsCRP (mg/l)	0.21 ± 0.27	0.21 ± 0.29	0.22 ± 0.30	0.23 ± 0.28	0.083	0.17 ± 0.24	0.18 ± 0.25	0.19 ± 0.24	0.23 ± 0.27	<0.01
Total cholesterol (mmol/l)	4.8 ± 0.9	5.0 ± 0.9	5.0 ± 0.9	5.1 ± 1.0	<0.01	4.8 ± 0.9	4.9 ± 0.9	5.0 ± 0.9	5.2 ± 1.0	<0.01
Triglyceride (mmol/l)	1.4 ± 0.8	1.7 ± 1.0	2.0 ± 1.2	2.5 ± 1.6	<0.01	1.3 ± 0.7	1.5 ± 0.7	1.6 ± 0.9	1.9 ± 1.1	<0.01
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	<0.01	1.3 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	<0.01
Fasting glucose (mmol/l)	4.8 ± 0.5	4.8 ± 0.6	4.8 ± 0.6	4.9 ± 0.7	<0.01	4.6 ± 0.5	4.6 ± 0.5	4.6 ± 0.5	4.7 ± 0.6	<0.01
2-h glucose (mmol/l)	6.0 ± 1.8	6.2 ± 1.8	6.4 ± 1.8	6.9 ± 1.9	<0.01	6.6 ± 1.6	6.6 ± 1.6	6.8 ± 1.6	7.2 ± 1.8	<0.01
Fasting insulin (pmol/l)	44.4 ± 25.7	47.2 ± 38.9	50.0 ± 27.8	54.2 ± 29.2	<0.01	52.1 ± 26.4	54.2 ± 35.4	55.6 ± 38.2	60.4 ± 34.0	<0.01
2-h insulin (pmol/l)	137.5 ± 138.2	149.3 ± 147.9	172.9 ± 161.8	222.9 ± 218.8	<0.01	190.3 ± 156.3	206.3 ± 186.1	220.9 ± 184.0	268.8 ± 263.2	<0.01
A1C (%)	5.5 ± 0.4	5.6 ± 0.4	5.6 ± 0.4	5.6 ± 0.4	<0.01	5.5 ± 0.4	5.5 ± 0.4	5.6 ± 0.4	5.7 ± 0.5	<0.01
HOMA-β	120.7 ± 138.3	127.1 ± 140.5	134.0 ± 116.6	136.3 ± 174.7	0.063	151.9 ± 144.7	168.1 ± 149.8	180.7 ± 175.7	179.8 ± 162.0	<0.01
HOMA-IR	1.4 ± 0.8	1.5 ± 1.3	1.5 ± 0.9	1.7 ± 1.0	<0.01	1.6 ± 0.8	1.6 ± 1.0	1.6 ± 1.2	1.8 ± 1.1	<0.01
QUICKI	0.74 ± 0.34	0.75 ± 0.34	0.75 ± 0.57	0.70 ± 0.34	0.015	0.70 ± 0.33	0.71 ± 0.28	0.74 ± 0.92	0.69 ± 0.28	0.058
Drinker (%)	66.9	70.0	71.0	72.7	<0.01	30.1	23.9	22.8	25.8	NS
Alcohol intake (kg)	6.42 ± 0.28	7.51 ± 0.35	7.73 ± 0.35	9.38 ± 0.40	<0.01	1.82 ± 0.18	1.42 ± 0.13	1.45 ± 0.13	1.99 ± 0.26	NS
Smoker (%)	51.5	46.0	48.6	51.7	NS	3.0	3.9	3.8	3.9	NS
Age and BMI adjusted	1.00	0.98 (0.55–1.74)	1.21 (0.68–2.14)	2.67 (1.59–4.47)	<0.001	1.00	0.94 (0.45–1.97)	1.50 (0.78–2.89)	2.06 (1.06–3.90)	0.034
Multivariate adjusted*	1.00	0.90 (0.49–1.61)	1.45 (0.81–2.45)	2.20 (1.28–3.73)	0.004	1.00	0.98 (0.46–2.10)	1.64 (0.85–3.18)	1.97 (1.03–3.77)	0.041

Data are means ± SD or RR (95% CI) unless otherwise indicated. *Adjusted for age, BMI, systolic blood pressure, family history of diabetes, smoking, alcohol and exercise status, fasting plasma glucose, triglyceride, HDL cholesterol, HOMA-IR, and hsCRP (high-sensitivity C-reactive protein). NS, not significant.

than that for ALT. However, we found no relationships when we used AST.

CONCLUSIONS — In this study, we found that the highest quartile of ALT activity was associated with risk of type 2 diabetes both cross-sectionally at baseline and prospectively at the 2-year follow-up period, as well as before and after adjusting for alcohol intake. We also demonstrated the independent predictive value of ALT activity on the incidence of type 2 diabetes after controlling for potential risk factors including age, family history, BMI, alcohol intake, and insulin resistance in both sexes. This result supports the previous studies reporting an association between abnormal liver function and type 2 diabetes, conducted mainly in Caucasian populations (2–5,7,9).

The liver is an important site for insulin clearance (13) and production of inflammatory cytokines (4,9). A large body of clinical and experimental data shows that increased flux of free fatty acids from increased visceral adipose tissue can lead to hepatic steatosis and insulin resistance (5). Other researchers have reported an association between elevated ALT activity and fatty liver (7,14) in obesity, insulin resistance, and type 2 diabetes (1). Another study has shown that ALT activity even within the normal range correlates with increasing hepatic fat infiltration (15). In contrast, elevated AST and GGT activities are not related to hepatic or whole-body insulin sensitivity (4). Although we did not confirm the presence of fatty liver by imaging, we showed a continuous relationship between ALT activity, lipid and glucose concentrations, HOMA-IR, HOMA-β, and QUICKI—all of which were independent predictors of type 2 diabetes.

Elevated liver enzyme activity may also reflect inflammation, which impairs insulin signaling (4). In agreement with other studies (16–18), our data show that individuals in the top ALT quartile have the highest levels of high-sensitivity C-reactive protein, which is also an independent predictor for type 2 diabetes (19).

In conclusion, in this population-based survey, increased activity of liver enzymes, notably ALT, was associated with a twofold increase in the risk of type 2 diabetes independently of conventional risk factors. Because the measurement of ALT activity is internationally standardized and often part of the routine clinical assessment, this marker may serve as a useful marker to identify individuals at high risk of type 2 diabetes in Asian populations.

Acknowledgments — This study was supported by the National Genome Research Institute, Seoul, Korea (2001-347-6111-221, 2002-347-6111-221, 2003-347-6111-221, 2004-347-6111-213, and 2005-347-24002-440-215).

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