Original Article

Liver Enzymes and Metabolic Risk Factors Including Diabetes Mellitus and Dyslipidemia in the Thai Adult Population

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Background: The elevation of liver enzymes, in the absence of viral hepatitis or heavy alcohol consumption, has been related to nonalcoholic fatty liver disease [NAFLD], which is associated with insulin resistance and metabolic syndrome**.**

Objective: To examine the association between liver enzymes and metabolic risk factors, including diabetes mellitus [DM] and dyslipidemia, in Thai adults.

Materials and Methods: A total of 4,317 adults were recruited from a health check-up clinic at Srinagarind Hospital, a tertiary care setting. After excluding previous history of all metabolic risk factors, liver disorder, vital hepatitis, and moderate to heavy alcohol drinking, body weight [BW], blood pressure [BP], fasting plasma glucose [FPG], total cholesterol [TC], triglyceride [TG], alanine aminotransferase [ALT], and aspartate aminotransferase [AST] were measured. The liver enzyme levels were categorized into quartiles and their associations with FPG, TC, TG, and prevalence of metabolic risk factors (including DM and dyslipidemia) were tested using multinomial logistic regression. Logistic regression was performed to calculate the odds ratio [OR] and 95% confidence interval [95% CI] of the relationship between liver enzymes and prevalence of each metabolic risk factor.

Results: Prevalence rates of elevated ALT and AST levels, defined as being more than twice of upper normal limit [UNL], in the entire cohort were 5.3 and 2.8%, respectively. After categorizing ALT and AST into quartiles, we found that the prevalence of DM, IFG, and hypertriglyceridemia were higher in the higher ALT and AST quartiles, but the magnitude of association was higher in ALT. After adjusting for age and BMI, every twofold elevation in ALT and AST was found to be associated with an increased risk for DM (OR 1.42, 95% CI: 1.23 to 1.63 vs. 1.35, 95% CI: 1.17 to 1.57), IFG (OR 1.49, 95% CI: 1.31 to 1.69 vs. 1.40, 95% CI: 1.22 to 1.62) and hypertriglyceridemia (OR 1.42, 95% CI: 1.29 to 1.56 vs. 1.22, 95% CI: 1.09 to 1.36), respectively). However, the elevations of ALT and AST were not associated with increased risk of hypertension or hypercholesterolemia in the present study.

Conclusion: Elevations in ALT and AST levels independently predict DM, IFG, and hypertriglyceridemia in Thai adults.

Keywords: Diabetes, Liver enzyme, Metabolic syndrome

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Elevation of liver enzymes, particularly serum alanine aminotransferase [ALT], in the absence of viral hepatitis or heavy alcohol consumption has been related to nonalcoholic fatty liver disease [NAFLD] and nonalcoholic steato-hepatitis [NASH][1-3]. This condition is associated with insulin resistance, obesity, central fat distribution, glucose intolerance, dyslipidemia, high blood pressure[4-7], and metabolic syndrome[8].

Prevalence of NAFLD, as well as that of diabetes mellitus [DM], are increasing in the Asia-Pacific region including Thailand[9]. Moreover,

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NAFLD is recognized as a hepatic manifestation of metabolic syndrome, which may predict DM and cardiovascular disease [CVD][10]. Previous studies have shown ALT concentration to be associated with DM independent of obesity[10,11]. Notwithstanding, the associations of liver enzymes with impaired fasting glucose [IFG] and other cardiovascular metabolic risks other than DM (i.e., hypertension [HT] and dyslipidemia) have received less attention, and there is a paucity of epidemiologic data in Thai adults. Therefore, this study was designed to determine the prevalence of elevated liver enzymes and its association with metabolic risks, including DM and dyslipidemia, in the Thai adult population.

Materials and Methods

Subjects and setting

The present study was designed as a cross-sectional investigation. The authors recruited the subjects from a health check-up clinic at Srinagarind Hospital, which is a tertiary care setting. Although the clinic was set up to serve the province's entire population, most of the clients who visit the clinic live around the capital district.

The study was formally approved by the Ethics Committee of Khon Kaen University and written informed consent was obtained from each individual involved. All patients who came to the clinic from 2005 to 2006 for health check-ups were invited to provide basic clinical information for the study. A total of 4,317 participants (1,694 men and 2,623 women) were included in the study. All participants were Thai. Patients were excluded from analysis if they were known to have DM, HT, dyslipidemia, or viral hepatitis, to engage in moderate to heavy alcohol consumption, or to be taking any medications for DM, HT, dyslipidemia or viral hepatitis.

Measurements

The participants were interviewed by a well-trained research nurse, who completed a questionnaire and an informed consent form. Each participant's body weight [BW] and standing height (without shoes) were measured using an electronic balance (accuracy 0.1 kg) and a stadiometer (nearest 0.1 cm), respectively. Body mass index [BMI] was calculated by dividing weight in kilograms [kg] by height^2 in square meters. Systolic blood pressure [SBP] and diastolic blood pressure [DBP] was measured twice in the left arm and recorded after the participant had been seated and resting for at least five minutes. The average of the two measurements was then used for all analyses.

Laboratory measurements

Serum samples were collected in the morning after participants had fasted for 12 hours. Blood samples were immediately centrifuged. Fasting plasma glucose [FPG], ALT, aspartate aminotransferase [AST], total cholesterol [TC], and triglycerides [TG] were included in the measurements. FPG levels were measured using the glucose oxidase method, while serum ALT, AST, TC, and TG were measured using enzymatic methods with an automatic autoanalyzer (Cobas Integra 800; Roche Diagnostics, Mannheim, Germany).

Operational definition

IFG was defined as FPG within 100 to 125 mg/dl and DM as FPG of 126 mg/dl or more in two consecutive tests within one week apart[12]. HT was defined as SBP of more than 140 mmHg or DBP of more than 90 mmHg[13]. Hypercholesterolemia and hypertriglyceridemia were defined as TC of 200 mg/dl or more and TG of 150 mg/dl or more, respectively. Obesity was defined as BMI $\geq$25 kg/m^2[14]. Elevated liver enzymes was defined as ALT or AST levels more than twice the upper normal limits [UNL][15], which were 36 and 32 unit/L for ALT and AST, respectively.

Statistical analysis

Statistical analysis was performed with Stata, version 10.1 (Stata, College Station, TX). Descriptive statistics were calculated for each sex separately. Results were expressed as mean and standard deviation [SD]. Prevalence was expressed as a percentage. The difference in baseline characteristics between men and women were tested using an unpaired t-test. Correlation between liver enzymes and each metabolic risk factor was analyzed using Pearson's correlation. In this study, the levels of liver enzymes were categorized into quartiles and the associations between liver enzymes and FPG, TC, TG, prevalence of IFG, DM, HT, and dyslipidemia were tested using multinomial logistic regression. Logistic regression was performed to calculate the odds ratio and 95% confidence interval (95% CI) between liver enzymes and prevalence of each metabolic risk factor.

Results

A total of 4,317 Thai participants, aged between 14 and 83 years (mean age of 49 and 47 years

Table 1. Characteristics of study subjects

Variables	Men (n = 1,694)	Women (n = 2,623)	Mean differences (95% CI)
Age (years)	49.4±11.0	47.0±10.4	2.4 (1.8 to 3.0)*
Weight (kg)	67.3±10.5	56.9±9.3	10.4 (9.8 to 11.0)*
Height (cm)	165.5±5.7	155.1±5.6	10.4 (10.1 to 10.8)*
Body mass index (kg/m^2)	24.6±3.5	23.7±3.8	0.9 (0.7 to 1.1)*
Systolic blood pressure (mmHg)	121.9±16.3	117.3±16.4	4.6 (3.6 to 5.6)*
Diastolic blood pressure (mmHg)	80.4±11.0	76.2±10.9	4.2 (3.5 to 4.9)*
Fasting plasma glucose (mg/dl)	96.1±31.0	88.8±20.6	7.3 (5.7 to 8.8)*
Total cholesterol (mg/dl)	212.6±43.6	211.2±42.5	1.4 (1.2 to 4.0)
Triglyceride (mg/dl)	163.1 to 119.0	115.6 to 76.1	47.5 (41.6 to 53.2)*
Alanine aminotransferase [ALT] (unit/l)	40.1 to 27.5	27.4 to 24.7	12.7 (11.1 to 14.3)*
Aspartate aminotransferase [AST] (unit/l)	31.8 to 21.5	25.4 to 17.5	6.4 (5.2 to 7.6)*

* p-value <0.05

for men and women, respectively) were recruited. On average, men were older, heavier, taller, than women and had higher BMI, SBP, and DBP. FPG, TG, ALT, and AST levels were also significantly higher in men than in women, while TC levels were comparable between the sexes (Table 1).

Serum ALT and AST were correlated with BMI, SBP, DBP, FPG, TC, and TG. However, the correlations were modest. Prevalence of elevated ALT and AST levels (more than twice the UNL) in the entire cohort were 5.3 and 2.8%, respectively. Prevalence of DM, IFG, HT, hypercholesterolemia, hypertriglyceridemia, and obesity were 3.8, 5.2, 25.9, 59.3, 29.8, and 35.8%, respectively. The prevalence of metabolic risk factors was significantly higher in men than in women (Table 2).

Serum ALT and AST levels were further categorized into quartiles. The prevalence of DM, IFG, and hypertriglyceridemia were significantly higher with higher ALT quartiles. The relative risk ratios [RRR] of the highest ALT quartile compared with the lowest quartiles for DM, IFG, and hypertriglyceridemia were 4.00, 3.84, and 3.91, respectively. Although the prevalence of HT and hypercholesterolemia were also higher with higher ALT quartiles, no association was demonstrated. Analysis of AST quartiles showed similar results to those regarding ALT. However, the magnitude of association with metabolic factors was clearly higher in ALT (Table 3).

Elevation of both ALT and AST significantly increased risk of DM, IFG, and hypertriglyceridemia. After adjustment for age and BMI, every twofold elevation of ALT increased the risk of DM, IFG, and hypertriglyceridemia by 1.42, 1.49, and 1.42, respectively, while every twofold elevation of AST increased the risk of DM, IFG, and hypertriglyceridemia by 1.35, 1.4, and 1.22, respectively. Despite the elevation of ALT significantly increased risk of hypercholesterolemia, this association lost statistical significance after adjustment with age and BMI. In this study, no association of elevated ALT or AST levels with hypertension was observed (Table 4).

Table 2. Prevalence of elevated liver enzymes and metabolic risk factors

Prevalence (%)	All	Men	Women
Elevated ALT	5.3	8.9*	2.9
Elevated AST	2.8	4.5*	1.7
Diabetes mellitus	3.8	5.1*	3.0
Impaired fasting glucose	5.2	7.4*	3.7
Hypertension	25.9	32.3*	21.8
Hypercholesterolemia	59.3	60.4*	58.6
Hypertriglyceridemia	29.8	42.3*	21.8
Overweight	35.8	42.6*	31.5

* p-value <0.05 vs. women

Discussion

Serum liver enzymes are one of the most important markers of fatty liver disease and metabolic syndrome. The present study examined the associations of serum liver enzymes on the prevalence of multiple risk factors for metabolic syndrome.The present study demonstrated that serum ALT was positively associated with increased risks of DM, IFG,

Table 3. Relative risk ratio (RRR) of each metabolic factor according to quartile groups of liver enzymes

RRR in each quartile	Q1	Q2	Q3	Q4
ALT (units/L)	≤17	18 to 26	27 to 40	≥41
Diabetes mellitus	1	2.13 (1.27 to 3.58)	3.90 (2.41 to 6.31)	4.00 (2.47 to 6.49)
Impaired fasting glucose	1	2.35 (1.59 to 3.47)	3.66 (2.53 to 5.31)	3.84 (2.65 to 5.56)
Hypertension	1	1.84 (1.50 to 2.25)	1.78 (1.45 to 2.18)	1.99 (1.62 to 2.45)
Hypercholesterolemia	1	1.20 (1.01 to 1.42)	1.61 (1.36 to 1.92)	1.51 (1.27 to 1.79)
Hypertriglyceridemia	1	1.86 (1.50 to 2.29)	2.74 (2.24 to 3.37)	3.91 (2.20 to 4.79)
AST (units/L)	≤20	21 to 24	25 to 30	≥31
Diabetes mellitus	1	1.20 (0.80 to 1.81)	1.39 (0.93 to 2.07)	1.81 (1.24 to 2.64)
Impaired fasting glucose	1	1.24 (0.89 to 1.73)	1.80 (1.31 to 2.45)	2.06 (1.52 to 2.79)
Hypertension	1	0.96 (0.77 to 1.19)	1.18 (0.96 to 1.45)	1.11 (0.96 to 1.46)
Hypercholesterolemia	1	1.17 (0.99 to 1.39)	1.42 (1.19 to 1.68)	1.15 (0.97 to 1.36)
Hypertriglyceridemia	1	1.50 (1.22 to 1.83)	2.29 (1.89 to 2.78)	2.97 (2.45 to 3.59)

and hypertriglyceridemia after adjusting for confounding factors (age and BMI). This finding was consistent with several cross-sectional studies, which reported a relationship between ALT and metabolic risk factors including DM[10,11,16-18] and dyslipidemia[19,20]. Similarly, AST was associated with increased risks of DM, IFG, and hypertriglyceridemia, which is consistent with the data reported by Hanley et al[17] and Hye-Ran Ahn et al[21]. However, the associations were less pronounced compared to those with ALT. This may be explained by the fact that AST is a less specific marker of liver function than ALT. Therefore, ALT measurement in clinical practice may be useful and more specific in detecting liver pathology related to metabolic syndrome.

Because the liver plays a critical role in the maintenance of carbohydrate homeostasis and insulin metabolism[22], it is not surprising that its functions may be associated with the risk of glucose intolerance and hypertriglyceridemia. According to the Third Report of the National Cholesterol Education Program [NCEP], raised TG levels are the key component of metabolic syndrome[23]. Unlike TG, raised low-density lipoprotein [LDL] cholesterol shows less association with insulin resistance and metabolic syndrome. This may explain why hypercholesterolemia, which is the overall amount of LDL, TG, and high-density lipoprotein [HDL], shows no significant association with elevated liver enzymes. In the current study, after adjustment for age and BMI, elevation of serum ALT and AST was not associated with the risk of hypertension. This finding was consistent with The Framingham Heart Study, which demonstrated a significant association between elevation of serum ALT and systolic blood pressure, but significance was lost after adjustment for BMI[18]. Previous reports have demonstrated that NAFLD is an independent risk factor for hypertension[24,25]. However, their findings may be due to insulin resistance, which is known as a definite risk factor in the development of both NAFLD and hypertension. To our knowledge, there is no direct linkage between serum transaminase level and prevalence of hypertension.

Some limitations in the present study is worth mentioning. First, this study had a cross-sectional design, so the causal relationships between liver enzyme elevation and metabolic risk factors could not be described. Second, these results relied on a single measurement of aminotransferase levels for each participant, so we were unable to account for interindividual variation with regard to these levels. This is also a concern with regard to the diagnoses of HT, because a single measurement of BP may be insufficient to diagnose this condition. Since the setting was a rural Thai province, these results may not be generalizable to urban populations or non-Asian populations, among whom lifestyle and demographic structure could differ from the present population. In addition, the study was undertaken in a health check-up clinic setting, meaning the prevalence of diabetes could be higher than the true prevalence in the general Thai population. However, a major strength of the present study is that the sample size was large enough to ensure that we could assess even modest effects. The diagnosis of DM and IFG was based on repeated fasting plasma glucose measurement, which minimized any possibility of misdiagnosis. Further prospective studies addressing the associations of ALT, AST, and other liver markers with risk of subsequent diabetes

Table 4. Odds ratio [OR] of twofold elevation of serum ALT and AST on each metabolic risk factor after adjusting for age and BMI

Metabolic risks	Diabetes mellitus	Impaired fasting glucose	Hypertension	Hypercholesterolemia	Hypertriglyceridemia
2 folds of ALT					
OR (95% CI)	1.34* (1.19 to 1.51)	1.39* (1.24 to 1.56)	1.08 (0.99 to 1.18)	1.13* (1.03 to 1.24)	1.53* (1.39 to 1.70)
Adjusted OR (95% CI)	1.42* (1.23 to 1.63)	1.49* (1.31 to 1.69)	1.02 (0.92 to 1.13)	1.09 (0.99 to 1.20)	1.42* (1.29 to 1.56)
2 folds of AST					
OR (95% CI)	1.30* (1.14 to 1.48)	1.34* (1.18 to 1.52)	1.06 (0.95 to 1.18)	0.99 (0.90 to 1.10)	1.26* (1.12 to 1.41)
Adjusted OR (95% CI)	1.35* (1.17 to 1.57)	1.40* (1.22 to 1.62)	1.01 (0.88 to 1.14)	0.96 (0.86 to 1.06)	1.22* (1.09 to 1.36)

* *p*-value <0.01

are warranted. In summary, the elevation of ALT and AST levels was positively associated with DM, IFG, and hypertriglyceridemia among Thai adults after excluding viral hepatitis and moderate to heavy drinking. Liver enzyme measurement may be a useful additional parameter in identifying patients at high probability of having metabolic risk factors.

What is already known on this topic?

ALT concentration is associated with DM independently of obesity.

What this study adds?

Elevation of ALT and AST levels were positively associated with DM, IFG, and hypertriglyceridemia among Thai adults. Liver enzyme measurement may be a useful additional parameter in identifying patients at high probability of having metabolic risk factors.

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Potential conflicts of interest

The authors declare no conflict of interest.

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