Abnormal Liver Enzymes in Thai Patients with Metabolic Syndromes

Mayuree Homsanit MD, MPH, PhD*, Anawin Sanguankeo**, Sikarin Upala**, Kamol Udol MD, MSc*

* Department of Preventive and Social Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok Thailand
** Medical student, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok Thailand

Objective: Elevated transaminases have been found to be associated with metabolic syndrome (MS) in many populations but little is known in Asians. The present study aimed to investigate the association between elevated hepatic enzymes in Thai patients diagnosed with MS.

Material and Method: A cross-sectional study on 2,585 Thais was conducted. Blood pressure, waist circumference, fasting plasma glucose, triglyceride, HDL-cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) were measured. MS was diagnosed using NCEP/ATP III criteria with modified waist circumference for Asian. The association between MS with elevated liver enzymes was performed using logistic regression.

Results: Twenty-seven percent of the subjects were found to have MS. The MS group had significantly higher mean AST, ALT, and ALP levels than the non-MS group (mean (SD) for AST 29.86 (18.97), 24.08 (12.71); ALT 38.39 (29.14), 24.38 (18.57); and ALP 73.45 (27.09), 65.72 (21.27) for MS and non-MS, respectively, p < 0.05). MS was significantly associated with elevated liver enzymes. The adjusted odds ratios (OR) were 2.2 (95% confidence interval (CI): 1.6-2.9), 2.3 (95% CI: 1.8-3.0), and 2.2 (95% CI: 1.1-4.2) for elevated AST, ALT, and ALP, respectively. ALT/AST ratio of ≥ 1 was significantly associated with MS in both genders (adjusted ORs: 1.72 (95% CI: 1.28-2.32) for men and 2.30 (95% CI: 1.68-3.16) for women).

Conclusion: There is a strong association between metabolic syndrome and elevated liver enzymes. Further study is needed to investigate the long-term sequelae of liver abnormalities in those with metabolic syndrome in Thai population.

Keywords: Metabolic syndrome, Elevated liver enzymes

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Metabolic syndrome (MS) is characterized by a clustering of cardiovascular risks, specifically insulin resistance, hypertension, abdominal obesity, and dyslipidemia. Its prevalence is 23.7% in US adults(1) and 15-23% in Thai adults using NCEP/ATP III criteria as a measurement(2-4). In addition to increasing risk of atherosclerotic cardiovascular disease, this condition has been found to be associated with liver abnormalities such as nonalcoholic fatty liver disease (NAFLD) in many populations(5-7) and may contribute to development of cirrhosis(6) and hepatocellular carcinoma(9).

Non-alcoholic fatty liver disease (NAFLD) is a type of chronic liver disease of which pathological changes are similar to those of alcoholic liver disease but can be found in people who are not heavy drinkers(10). The liver damage spectrum ranges from a simple steatosis, the mildest form, to non-alcoholic steatohepatitis (NASH), a fatty liver with inflammation and evidence of damage to hepatocytes, to cirrhosis and to the extreme form, hepatocellular carcinoma or liver failure(11). At present, NAFLD is considered a hepatic manifestation of metabolic syndrome with insulin resistance(12,13).

Non-alcoholic steatohepatitis (NASH) is described as a type of liver injury of which histologic change mimics that of alcoholic hepatitis, and is found in patients without a history of alcohol abuse(14). It significantly increases mortality and risk of developing end-stage liver disease(15). A previous study showed an association between NASH and...
metabolic syndrome. Additionally, diabetes and hypertensive conditions also sharply increase the prevalence of NASH, compared to those who have neither factor. Although the gold standard for diagnosis of NAFLD is liver biopsy, however, the diagnosis of this condition in clinical practice is usually based on clinical assessment with the finding of abnormal liver enzymes.

A survey in the US demonstrated that conditions associated with NAFLD, such as obesity and dyslipidemia, were associated with unexplained abnormal aminotransferase levels in US adults. Several studies have revealed a positive correlation between metabolic syndrome components and elevated liver enzymes including alanine aminotransaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT). In Thailand, a study by Kladchareon et al identified the prevalence of NASH in 46 Thai patients, with non-HBV, non-HCV chronic hepatitis and found that 76.1% of the patients had NASH. However, little is known about how each metabolic syndrome component affects the risk of elevated liver markers in a general population without the clinical syndrome of hepatitis. Moreover, diagnosis of NASH by liver biopsy in large scale may not be cost-effective and may bring about the complication from the procedure. The present study was conducted to investigate abnormal liver enzymes including elevated AST, elevated ALT, and elevated ALP in patients with metabolic syndrome who did not have clinical syndrome of hepatitis, and to compare the association of each metabolic syndrome component with these liver abnormalities.

Material and Method
Participants were drawn from 3,630 Thai subjects who received annual health examinations at the Department of Preventive and Social Medicine, Siriraj Hospital, Mahidol University in Bangkok Thailand. In the present study, 2,585 subjects aged 35 years or older were enrolled. Subjects who were under 35 years of age were excluded due to inadequate information and too small number for analysis. Participants with history of hepatitis, those with alcohol use, and subjects with missing data were excluded. Overall, 1291 men (49.9%) and 1294 women (50.1%) whose ages ranged from 35 to 75 years were included. The present study was approved by Siriraj Institutional Review Board (Certificate of Approval No. Si 204/2009).

Power determination
Miyatake et al found a higher mean AST level in Japanese people with MS compared to those without (29.6 ± 12.9 U/L and 24.7 ± 9.7 U/L for those with MS and non-MS, respectively). The lowest prevalence of MS in Thailand has been found to be 15%. Therefore, 2585 subjects would provide at least 387 with MS, which allowed more than 90% power in determination of difference in mean AST between those with and without MS.

Data collection

Demographic information
Demographic information, alcohol drinking, and history of hepatitis from any cause were obtained through patient interviews. Subjects with history of alcohol use and hepatitis were excluded from the analysis.

Physical examination and anthropometric measurement
Physical examination included the measurement of systolic and diastolic blood pressure. Anthropometric measurement including body weight (kg), height (cm), and waist circumference (cm) was obtained with the patient standing in undergarments with his/her hands at side. Waist circumference was measured at the iliac crest level during normal end-expiration with the measuring tape in a horizontal plain. Body mass index (BMI) (kg/m²) was also calculated.

Laboratory
Blood samples were obtained after a 12-hour fasting session. Biochemical analysis of the blood samples was performed for fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), ALT, AST, and ALP levels using standard methods.

Diagnosis of metabolic syndrome and abnormal liver function
Metabolic syndrome was diagnosed as presence of three or more of the following criteria, according to NCEP/ATP III with modified waist circumference for Asian: 1) waist circumference ≥ 90 cm in men or ≥ 80 cm in women, 2) TG ≥ 150 mg/dL or taking TG lowering drug, 3) HDL-c < 40 mg/dL in men, < 50 mg/dL in women or taking HDL-c increasing drug, 4) SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or taking...
antihypertensive drugs, and 5) FPG ≥ 100 mg/dL or taking antihyperglycemic drugs. Increased liver enzyme was defined as AST, ALT, or ALP level of more than upper normal limits of the laboratory values (AST > 37 IU/L, ALT > 40 IU/L or ALP > 117 IU/L).

Statistical analysis

Demographic characteristics, anthropometric measurement, and laboratory results were described as proportion or mean and standard deviation as appropriate. Chi-square and unpaired t-test were used to determine the difference in these parameters between male and female, and between MS and non-MS subjects with p < 0.05 was set for significant difference. Waist circumference, TG, SBP, DBP, HDL-c, and FPG were categorized according to the modified MS criteria for Asian as mentioned earlier. Liver enzymes were categorized to normal or elevated if the enzymes were found to be higher than upper normal limit. Univariate analyses were performed to investigate the association between each metabolic syndrome component with elevated liver enzymes, and between MS with elevated liver enzymes. The effect of age and gender was adjusted by multivariate analyses. All statistical analyses were performed using Stata™ version 8.0 (College Station, Texas).

Results

Subject characteristics

The clinical and biochemical characteristics of 1,291 men (49.9%) and 1294 women (50.1%) enrolled in the present study are shown in Table 1. Twenty-seven percent of the subjects had metabolic syndrome using modified NCEP/ATP III criteria for Asian. The prevalence of MS was higher in men (33.2%) than in women (20.8%). The highest prevalence of MS was found in the age group of 60 years or older in both genders. The prevalence of MS also increased with increasing age in women (test for trend, p < 0.01). Generally, the participants with MS defining abnormalities had higher various metabolic factors in both genders, i.e., BMI, waist circumference, SBP, DBP, fasting plasma glucose, and triglyceride than those without MS-defining abnormalities. HDL-c was lower in those with MS in both genders but LDL-c was significantly higher in women with MS but not in men. The levels of AST, ALT, and ALP were also significantly higher in subjects with MS. The ALT/AST ratio was also significantly higher in MS subjects in both genders. Fig. 1 shows the proportion of subjects with metabolic syndrome components in men and women. Men had significantly higher prevalence of elevated BP, FPG,
and TG while women had higher prevalence of low HDL-c and large waist circumference. The prevalence of participants with abnormal liver enzymes according to presence of MS is shown in Fig. 2. The proportions of high AST were 22.14%, 11.72% (p < 0.001); high ALT: 36.16%, 18.56% (p < 0.001); and high ALP: 2.09%, 2.08% (p = 0.43) in men with MS and non-MS, respectively. For women, the proportions of high AST were 12.64%, 2.73% (p < 0.001); high ALT 21.19%, 4.68% (p < 0.001); and high ALP 3.35%, 1.17% (p = 0.012) in those with MS and non-MS, respectively.

**MS components and association with abnormal liver enzymes**

Fig. 3 shows prevalence of elevated liver enzymes, which increased with number of MS component. When analysis was performed according to the number of MS component, it was found that the prevalence of elevated liver enzymes increased with increasing number of MS component. The proportion of elevated ALT increased about seven-fold from zero to five components in both genders (9.5% to 64.52% in men and 3.72% to 26.92% in women). For AST, the increment by four-fold was found in men (5.00% to 19.35%) and nine-fold in women (2.93% to 26.91%). There was also a linear trend of increased proportion in most liver enzymes with increasing numbers of MS components (test for trend, p < 0.01 except for ALP among men). Logistic regression analysis to identify the association of independent MS component, number of MS component, and increased hepatic enzymes in the present study population was performed. The results are shown in Table 2. After adjusting for age and BMI, the present noted statistically significant positive associations of AST and ALT levels with increased serum triglyceride and fasting plasma glucose in both genders. There was no significant association of MS component with ALP. The strength of association of MS component with AST and with ALT increased when MS components increased from two to five components in both genders. The same result was not found for number of MS components with ALP. Note that the association in women is stronger than in men.

Since high TG and high FPG were found to be significantly associated with abnormal AST and ALT, the authors explored the presence of both high TG and high FPG in prediction of elevated liver enzymes. After adjustment for age and BMI, elevated FPG combined with elevated TG were the strongest predictive criterion for elevated ALT (OR 3.5, 95% CI 2.4-4.9; OR 6.7, 95% CI 3.7-12.2 for men and women respectively, data not shown). Combination of other MS component shows no significant association with elevated liver enzymes. High ALT and high AST were significantly associated with MS in both genders as shown in Table 3, however, high ALP was significantly associated with MS only in women. When considering ALT/AST ratio as a marker of hepatic steatosis, this parameter also showed significant positive association with MS in both men and women. Moreover, subgroup analysis in subjects with normal AST and normal ALT levels showed that the ALT/AST
The present study found a strong association between metabolic syndrome and abnormal liver enzymes in this Thai population who showed no clinical signs of liver disease. Subjects with MS had significantly higher liver enzymes as determined by AST, ALT, and ALP in both genders. The prevalence of elevated AST and ALT levels in subjects with metabolic syndrome was two-fold and about six-fold of those without the syndrome in men and women, respectively. However, the association of elevated ALP and MS was less prominent compared to that of MS with elevated AST and ALT. The prevalence of MS in this study was 27%, slightly higher than previous studies in Thailand, which revealed the prevalence of MS about 15% to 23% (2-4). Given the adult population in Thailand aged 35 years or older of almost 30 million in the year 2008 (28), the burden of metabolic syndrome in Thailand might reach 8 million. The present study found that 35% of subjects with metabolic syndrome had elevated AST, ALT, or ALP level. Therefore, 2.8 million Thai people might be living with chronic subclinical liver disease associated with metabolic syndrome. The common cause of abnormal liver function found in metabolic syndrome and obesity is non-alcoholic fatty liver disease (NAFLD) characterized by elevation in AST and ALT levels. A study in Japanese subjects also found that ALT/AST ratio was higher in men and women with MS and the ratio could be an index for visceral fat accumulation (29). The ALT/AST ratio of 0.8 was also shown to be a marker of NAFLD (30). The present study found a comparable result that Thai men and women with MS had higher ALT/AST ratio and the ratio of > 1 was significantly associated with MS in both genders. This liver abnormality can progress to liver cirrhosis and hepatocellular carcinoma over a period of 10-year in 10% to 15% of patients (31). Moreover, the abnormality in liver transaminases was also found in those who had some components of MS but had not reached diagnostic criteria for the syndrome, and the prevalence of elevated transaminases increased with the increased number of MS components (test for trend, p < 0.01). The prevalence of subjects with 1-2 MS components in the present study was 51%, which might further increase the burden of NASH in Thailand.
and abnormal liver function\textsuperscript{(32-35)}. Impaired fasting glucose (IFG), the fasting glucose level of $\geq 100$ mg/dL, which is the result of insulin resistance state was found in 27% of the presented subjects (data not shown). The present study found that IFG has significant association with elevated transaminases (adjusted ORs 2.9 and 1.8 for elevated AST and ALT respectively, $p < 0.05$). Another feature of insulin resistance, hypertriglyceridemia, is the result of defect in lipid metabolism such as decrease lipoprotein lipase activity and increase hepatic VLDL production\textsuperscript{(37)}. Hypertriglyceridemia was found in 32% of the presented subjects (data not shown) and had significant association with elevated transaminases (adjusted ORs 2.3 and 2.2 for elevated AST and ALT respectively, $p < 0.05$). Combination of IFG and hypertriglyceridemia resulted in a higher chance of having liver function abnormality in both genders.

Limitation of the present study includes use of a cross-sectional study design, which cannot demonstrate temporal relationship between the metabolic abnormalities and elevated liver enzymes. Exclusion of other causes of liver disease, \textit{i.e.} alcohol consumption and history of hepatitis from any cause, was performed by interview, which may result in non-response or recall bias. However, the finding of abnormal liver function in those with metabolic syndrome and in those with presence of some metabolic syndrome component was evident and consistent with findings from other studies. The result of the present study should alert public health intervention for management of metabolic syndrome to prevent its potential sequelae including chronic liver disease and also warrant more extensive research in the future for better knowledge of this condition.

### Potential conflicts of interest

None.

### References


<table>
<thead>
<tr>
<th>Liver enzymes</th>
<th>Adjusted OR: all subjects (95% CI)</th>
<th>Adjusted OR: men (95% CI)</th>
<th>Adjusted OR: women (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>High AST</td>
<td>2.15 (1.56-2.91)</td>
<td>1.69 (1.19-2.40)</td>
<td>4.25 (2.32-7.80)</td>
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<tr>
<td>High ALT</td>
<td>2.32 (1.81-2.98)</td>
<td>1.91 (1.42-2.57)</td>
<td>3.66 (2.28-5.89)</td>
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<tr>
<td>High ALP</td>
<td>2.10 (1.09-4.04)</td>
<td>1.48 (0.62-3.48)</td>
<td>3.45 (1.28-9.31)</td>
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<td>ALT/AST ratio: $\geq 1$ vs. $&lt; 1$</td>
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<tr>
<td>All subjects</td>
<td>1.97 (1.59-2.46)</td>
<td>1.72 (1.28-2.32)</td>
<td>2.30 (1.68-3.16)</td>
</tr>
<tr>
<td>Subjects with normal ALT and AST</td>
<td>1.76 (1.37-2.25)</td>
<td>1.60 (1.13-2.27)</td>
<td>1.94 (1.37-2.74)</td>
</tr>
</tbody>
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### Table 3. Abnormal liver enzymes as predictors for metabolic syndrome
ความผิดปกติของค่าเอนไซม์ตับในผู้ป่วยชาวไทยที่มีภาวะกลุ่มอาการเมตะบอลิค

มุรี หอมสนิท, อนุวิล สงวนแก้ว, สิขริณญ์ อุปะละ, กมล อุดล

วัตถุประสงค์: ค่าเอนไซม์ตับที่สูงกว่าปกติพบว่ามีความสัมพันธ์กับกลุ่มอาการเมตะบอลิค (metabolic syndrome, MS) ในหลายเชื้อชาติแต่ข้อมูลนี้ในชาวเอเชียยังมีน้อย การศึกษานี้เพื่อศึกษาความสัมพันธ์ระหว่างค่าเอนไซม์ตับที่สูงกว่าปกติในผู้ป่วยชาวไทยที่ได้รับการวินิจฉัยกลุ่มอาการเมตะบอลิค

วิสัยและวิธีการ: ศึกษาแบบตัดขวางในชาวไทย 2,585 คน โดยบันทึกข้อมูลความดันโลหิต, รอบเอว, ระดับน้ำตาล, triglyceride, HDL-cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), และ alkaline phosphatase (ALP) วินิจฉัย MS โดยใช้เกณฑ์ NCEP/AIP III ที่ปรับเกณฑ์รอบเอวสำหรับชาวเอเชีย การวิเคราะห์ความสัมพันธ์ระหว่าง MS และค่าเอนไซม์ตับทำโดย logistic regression

ผลการศึกษา: ผู้เข้าร่วมศึกษาร้อยละ 27 มีลักษณะเข้าได้กับ MS กลุ่ม MS มีค่าเฉลี่ยของ AST, ALT, และ ALP สูงกว่ากลุ่มที่ไม่เป็น MS อย่างมีนัยสำคัญทางสถิติ (mean ± SD ของ AST 29.86 ± 18.97, 24.08 ± 12.71; ALT 38.39 ± 29.14, 24.38 ± 18.57; และ ALP 73.45 ± 27.09, 65.72 ± 21.27 สำหรับกลุ่มที่เป็นและไม่เป็น MS ตามลำดับ, p < 0.05) ภาวะ MS มีความสัมพันธ์กับการมีค่าเอนไซม์ตับสูงกว่าปกติอย่างมีนัยสำคัญทางสถิติ โดยมี adjusted OR (95%CI) ทำกับ 2.2 (1.6-2.9), 2.3 (1.8-3.0), และ 2.2 (1.1-4.2) สำหรับ AST, ALT, และ ALP ที่สูงกว่าปกติตามลำดับ ยิ่งมีสูงขึ้น ค่า MS อย่างมีนัยสำคัญทางสถิติ (adjusted ORs: 1.72 (1.28-2.32) และ 2.30 (1.68-3.16) สำหรับ AST และ ALPตามลำดับ)

สรุป: การศึกษานี้แสดงให้เห็นค่าเอนไซม์ตับสูงกว่าปกติในผู้ป่วยที่มี MS และมีความสัมพันธ์กับการมี MS ซึ่งมีประโยชน์ทางการแพทย์อย่างมาก

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