Abdominal obesity validates the association between elevated alanine aminotransferase and newly diagnosed diabetes mellitus

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Abstract. To examine how elevated alanine aminotransferase (ALT) could be associated with newly diagnosed diabetes mellitus. We conducted a cross-sectional analysis on a mass health examination. The odds ratios (ORs) for diabetes mellitus and newly diagnosed diabetes mellitus were compared between people with and without abdominal obesity, together with and without elevated ALT levels. 5499 people were included in this study. Two hundred fifty two (4.6%) fulfilled the diagnosis of diabetes mellitus with 178 (3.2%) undiagnosed before. Metabolic syndrome was vigorously associated with diabetes mellitus and newly diagnosed diabetes mellitus (12.4% vs. 1.4% and 9.0% vs. 0.9%), but elevated ALT alone was not. However, coexisting with obesity, elevated ALTs were robustly associated with diabetes mellitus and newly diagnosed diabetes mellitus. For the incidence of newly diagnosed diabetes mellitus, in comparison to non-obese people with normal ALT (1.7%, OR = 1), obese people especially with elevated ALT levels had significantly higher ORs (obese with ALT ≤ 40 U/L: 4.7%, OR 1.73, 95% CI 1.08-2.77, P < 0.023; ALT 41-80 U/L: 6.8%, OR 2.06, 95% CI 1.20-3.55, P < 0.009; ALT 81-120 U/L: 8.8%, OR 3.07, 95% CI 1.38-6.84, P < 0.006; ALT > 120 U/L: 18.2%, OR 7.44, 95% CI 3.04-18.18, P < 0.001). Abdominal obesity validates the association between elevated alanine aminotransferase and diabetes mellitus and newly diagnosed diabetes mellitus. People with abdominal obesity, especially with coexisting elevated ALT levels should be screened for undiagnosed diabetes mellitus.

Keywords: Abdominal obesity, Alanine aminotransferase, Diabetes mellitus, Metabolic syndrome

DIABETES MELLITUS is a chronic debilitating disease. It creates a major challenge for modern health care systems because of its marked and growing prevalence. The longer the disease exists, especially if inadequately treated, the more complicated its co-morbidities may become. As a significant proportion of diabetes mellitus is undiagnosed [1-4], any possible symptom or sign associated with diabetes mellitus should not be neglected. In this regard, metabolic syndrome is well linked with type 2 diabetes mellitus and may be regarded as a warning of diabetes mellitus. However, the high prevalence of metabolic syndrome [5-7] may reduce its potency to motivate people to take appropriate modification of lifestyle or early medical interventions [8-10]. Therefore, subdividing metabolic syndrome further or adding other parameters to screen out subgroups at even higher risk for development of diabetes mellitus seems desirable and practical.

Besides metabolic syndrome features, hepatocytic enzymes are ones of the most frequently-identified laboratory parameters associated with insulin resistance [11-17]. Vozarova et al. reported that elevated alanine aminotransferase (ALT) levels were cross-sectionally associated with obesity and whole-body and
hepatic insulin resistance, and prospectively associated with a decline in hepatic insulin sensitivity and the development of type 2 diabetes mellitus [12]. Sattar et al. and Hanley et al. inferred that high ALT, even within normal range, was associated with insulin resistance independent of conventional metabolic measures, and might predict incident diabetes mellitus [13, 14]. Bonnet et al. disclosed that plasma concentration of gamma-glutamyltransferase (GGT) and ALT were inversely related with insulin sensitivity [15]. A 9-year of prospective following study performed by Doi et al. also suggested serum GGT and ALT concentrations could be used as predictors of diabetes mellitus in general population, independent of known risk factors [16]. Chen et al. even found that obesity coexisting with elevated ALT had higher odds than metabolic syndrome per se to have high homeostasis model assessment values [18]. However, there were controversies among these studies. For example, Perry et al. and Doi et al. reported a positive association between GGT levels and risk of type 2 diabetes mellitus, which was opposed by Vozarova et al.’s conclusion “higher ALT but not aspartate aminotransferase (AST) or GGT, predicted diabetes” [12, 16, 17]. Our previous study also found that elevated ALT was associated with metabolic syndrome and abdominal obesity but not independently associated with impaired fasting glucose or type 2 diabetes mellitus [19]. Given that elevated ALT may sometimes reflect an underlying insulin resistance, and is associated with whole body adiposity, it is worth verifying whether elevated ALT could offer synergistic effect on metabolic syndrome characteristic features for predicting new-onset diabetes mellitus in a larger population. We hereby conducted this study to investigate if elevated ALT could further raise the odds in obese people to have diabetes mellitus or newly diagnosed diabetes mellitus.

**Research Design and Methods**

Being approved by Institutional Review Board (Document number: IRB 102-1014B), we conducted a cross-sectional analysis on decoding profiles extracted from a mass health examination which was performed on employees in an industrial park in middle Taiwan in July and August 2012. Self-reported medical history (including diseases like diabetes mellitus, hypertension, dyslipidemia, viral hepatitis, etc., and medication currently prescribed, smoking and alcoholic use) was recorded by standardized questionnaires and was confirmed by a nurse-administered check-up. Eventually, there were 5499 people included in this study. The odds ratios (ORs) for diabetes mellitus and newly diagnosed diabetes mellitus were calculated and compared between people with or without metabolic syndrome and abdominal obesity, respectively, and further subdivided with different incremental levels of ALT.

**Diagnostic criteria for metabolic syndrome**

Metabolic syndrome was defined by the criteria harmonized by AHA/NHLBI Scientific Statement [20], which was the presence of at least three of the following:

1. Abdominal obesity: waist circumference ≥ 90 cm (35 in) in men or ≥ 80 cm (32 in) in women,
2. Fasting glucose ≥ 5.6 mmol/L (100 mg/dL) (or receiving drug therapy for hyperglycemia),
3. Serum triglycerides ≥ 1.7 mmol/L (150 mg/dL),
4. Serum HDL-C < 1.04 mmol/L (40 mg/dL) in men or < 1.30 mmol/L (50 mg/dL) in women,
5. Systolic blood pressure (BP) ≥ 130 mmHg or diastolic BP ≥ 85 mmHg (or receiving drug therapy for hypertension).

BP higher than 130/85 mmHg was confirmed by at least two assessments with a resting interval longer than 15 minutes. Therapy for dyslipidemia was not considered as the criteria because of various types and standards of serum lipid levels for patients to initiate and adjust their medical treatment. Fasting plasma glucose between 5.6 to 6.9 mmol/L (100 to 125 mg/dL) was regarded as impaired fasting glucose and higher than 6.9 mmol/L (125 mg/dL) as diabetes mellitus.

**Definition of diabetes mellitus and newly diagnosed diabetes mellitus**

Fasting plasma glucose higher than 6.9 mmol/L or receiving drug therapy for hyperglycemia was regarded as diabetes mellitus. Without diabetes mellitus history, fasting plasma glucose higher than 6.9 mmol/L was regarded as newly diagnosed diabetes mellitus.

**ALT measurement**

Only ALT was measured, without analysis of other liver function tests, in this health examination. The ALT levels were subdivided into 4 groups (within normal limit: ALT ≤ 40 IU/L; within 2 times elevated: 40 IU/L < ALT ≤ 80 IU/L; 2-3 times elevated: 80 IU/L < ALT ≤ 120 IU/L and above 3 times elevated: ALT > 120 IU/L).
Statistical analysis

Logistic regression in SPSS was used to examine the association between diabetes mellitus/newly diagnosed diabetes mellitus and metabolic syndrome and abdominal obesity, together with or without elevated ALT levels. All data were shown as mean ± standard error. All the ORs were calculated with adjustment for age (as a continuous variable) and sex, showing 95% confidence interval (CI) of OR. A p value less than 0.05 and a 95% confidence interval of OR not containing 1 was considered statistically significant.

Result

Demographic of people studied

The mean age of the 5499 people (231 women, 4.2%) was 40.1 ± 6.3 years. The mean BMI was 25.2 ± 3.6. The demographics and characteristics of the people studied were summarized by age in Table 1, and by ALT levels in Table 2. There were 1793 (32.6%) people with abdominal obesity, 3354 (61.0%) with high blood pressure (i.e. BP ≥ 130/85 mmHg; but only 1922, 35.0%, had real hypertension, i.e. BP ≥ 140/90 mmHg or have being received drug therapy for hypertension), 1983 (36.1%) with high triglycerides (≥ 1.7 mmol/L), 910 (16.5%) with low HDL-C (< 1.04 mmol/L in men or < 1.30 mmol/L in women), 1739 (31.6%) with elevated fasting glucose (i.e. fasting glucose ≥ 5.6 mmol/L or 100 mg/dL; but just 595, 10.8%, with fasting glucose ≥ 6.1 mmol/L or 110 mg/dL), 1596 (29.0%) with metabolic syndrome (but only 1275, 23.2% fulfilled metabolic syndrome criteria defined by WHO). There were 252 (4.6%) people fulfilled the diagnosis of diabetes mellitus, and 178 of them (3.2%) were undiagnosed before.

Combination of abdominal obesity and incremental elevation of ALT was associated with newly diagnosed diabetes mellitus

The prevalence of elevated ALT was high at 23.9% (1062, 19.3% with an ALT level between 41 and 80 U/L; 180, 3.3% between 81 and 120 U/L; 69, 1.3% higher than 120 U/L). Older people were more likely to have newly diagnosed diabetes mellitus. Compatible with

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>24-29</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-75</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of people</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Woman</td>
<td>90 (1.6%)</td>
<td>2924 (53.2%)</td>
<td>2085 (37.9%)</td>
<td>321 (5.8%)</td>
<td>79 (1.4%)</td>
<td>5499 (100%)</td>
</tr>
<tr>
<td>Man</td>
<td>0</td>
<td>172 (5.9%)</td>
<td>54 (2.6%)</td>
<td>5 (1.6%)</td>
<td>0</td>
<td>231 (4.2%)</td>
</tr>
<tr>
<td>Abdominal Obesity</td>
<td>90 (100%)</td>
<td>2752 (84.1%)</td>
<td>2031 (63.4%)</td>
<td>316 (98.4%)</td>
<td>79 (100%)</td>
<td>5268 (95.8%)</td>
</tr>
<tr>
<td>High Blood Pressure</td>
<td>24 (26.7%)</td>
<td>967 (33.1%)</td>
<td>691 (33.1%)</td>
<td>93 (29.0%)</td>
<td>18 (22.8%)</td>
<td>1793 (32.6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47 (52.2%)</td>
<td>1705 (58.3%)</td>
<td>1321 (63.4%)</td>
<td>225 (70.1%)</td>
<td>56 (70.9%)</td>
<td>3354 (61%)</td>
</tr>
<tr>
<td>High TG</td>
<td>22 (44.4%)</td>
<td>895 (50.6%)</td>
<td>808 (56.8%)</td>
<td>158 (49.2%)</td>
<td>39 (49.4%)</td>
<td>1922 (35.0%)</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>14 (15.6%)</td>
<td>990 (33.9%)</td>
<td>819 (39.3%)</td>
<td>125 (38.9%)</td>
<td>35 (44.3%)</td>
<td>1993 (36.1%)</td>
</tr>
<tr>
<td>High Fasting Glucose</td>
<td>7 (7.8%)</td>
<td>457 (15.6%)</td>
<td>386 (18.5%)</td>
<td>49 (15.3%)</td>
<td>11 (13.9%)</td>
<td>910 (16.5%)</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>12 (13.3%)</td>
<td>793 (27.1%)</td>
<td>728 (34.9%)</td>
<td>159 (49.5%)</td>
<td>47 (59.5%)</td>
<td>1739 (31.6%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (12.2%)</td>
<td>781 (26.7%)</td>
<td>660 (31.7%)</td>
<td>117 (36.4%)</td>
<td>27 (34.2%)</td>
<td>1596 (29.0%)</td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0%)</td>
<td>90 (3.1%)</td>
<td>120 (5.8%)</td>
<td>31 (9.7%)</td>
<td>11 (13.9%)</td>
<td>252 (4.6%)</td>
</tr>
<tr>
<td>Newly diagnosed</td>
<td>0 (0%)</td>
<td>74 (2.5%)</td>
<td>83 (4.0%)</td>
<td>15 (4.7%)</td>
<td>6 (7.6%)</td>
<td>178 (3.2%)</td>
</tr>
</tbody>
</table>

The data are shown in number of people followed by percentage. High blood pressure means BP ≥ 140/90 mmHg. Low HDL-C means HDL-C < 1.04 mmol/L (40 mg/dL) in men or < 1.30 mmol/L (50 mg/dL) in women. High fasting glucose means fasting plasma glucose higher than 5.6 mmol/L (100 mg/dL). TG, triglyceride; HDL-C, high density lipoprotein cholesterol; ALT, alanine aminotransferase.
As shown in Table 2, with further adjustment for BMI, high blood pressure, high serum triglyceride, low HDL-C and viral hepatitis history, obese people with elevated ALT had significantly higher odds to have newly diagnosed diabetes mellitus (non-obese people with normal ALT, 1.7% as reference; ALT ≤ 40 U/L: 4.7%, OR 1.73, 95% CI 1.08-2.77, P = 0.023; ALT 41-80 U/L: 6.8%, OR 2.06, 95% CI 1.20-3.55, P = 0.009; ALT 81-120 U/L: 10.6%, OR 3.00, 95% CI 1.88-4.78, P < 0.001; ALT > 120 U/L: 17.0%, OR 5.68, 95% CI 3.03-10.7, P < 0.001).

**Table 2** Demographics and Characteristics of the Studied Subjects by ALT (U/L)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ALT ≤40 n (%)</th>
<th>40&lt; ALT ≤80 n (%)</th>
<th>80&lt; ALT ≤120 n (%)</th>
<th>ALT &gt; 120 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of people</td>
<td>4188 (76.2%)</td>
<td>1062 (19.3%)</td>
<td>180 (3.3%)</td>
<td>69 (1.3%)</td>
</tr>
<tr>
<td>Woman</td>
<td>221 (95.7%)</td>
<td>7 (3.0%)</td>
<td>2 (0.9%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Man</td>
<td>3967 (75.3%)</td>
<td>1055 (20.0%)</td>
<td>178 (3.4%)</td>
<td>68 (1.3%)</td>
</tr>
<tr>
<td>Abdominal Obesity</td>
<td>1048 (25.0%)</td>
<td>587 (55.3%)</td>
<td>114 (63.3%)</td>
<td>44 (63.8%)</td>
</tr>
<tr>
<td>High Blood Pressure</td>
<td>2874 (68.6%)</td>
<td>889 (83.7%)</td>
<td>156 (86.7%)</td>
<td>57 (82.6%)</td>
</tr>
<tr>
<td>High TG (≥ 150 mg/dL)</td>
<td>1246 (29.8%)</td>
<td>598 (56.3%)</td>
<td>106 (58.9%)</td>
<td>33 (47.8%)</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>577 (13.8%)</td>
<td>270 (25.4%)</td>
<td>43 (23.9%)</td>
<td>20 (29.0%)</td>
</tr>
<tr>
<td>High Fasting Glucose</td>
<td>1203 (28.7%)</td>
<td>430 (40.5%)</td>
<td>74 (41.4%)</td>
<td>32 (46.4%)</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>908 (21.7%)</td>
<td>543 (51.1%)</td>
<td>106 (58.3%)</td>
<td>39 (56.5%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Yes</td>
<td>151 (3.6%)</td>
<td>72 (6.8%)</td>
<td>18 (10.0%)</td>
</tr>
<tr>
<td></td>
<td>Newly diagnosed</td>
<td>102 (2.4%)</td>
<td>52 (4.9%)</td>
<td>15 (8.3%)</td>
</tr>
</tbody>
</table>

The data are shown in number of people followed by percentage. High blood pressure means BP ≥ 130/85 mmHg. Low HDL-C means HDL-C < 1.04 mmol/L (40 mg/dL) in men or < 1.30 mmol/L (50 mg/dL) in women. High fasting glucose means fasting plasma glucose higher than 5.6 mmol/L (100 mg/dL). TG, triglyceride; HDL-C, high density lipoprotein cholesterol; ALT, alanine aminotransferase.

**Fig. 1** Comparisons of the odds ratios for the incidence of newly diagnosed diabetes mellitus in relation to abdominal obesity and elevation of ALT. The odds ratios (with their 95% confidence intervals) of non-obese groups are shown with diamond shaped media, and the obese groups with round shaped media. All odds ratios were adjusted for age, sex, BMI, high blood pressure, high serum triglyceride, low HDL-C and viral hepatitis history. ALT levels are shown in U/L.

As shown in Fig. 1, with further adjustment for BMI, high blood pressure, high serum triglyceride, low HDL-C and viral hepatitis history, obese people with elevated ALT had significantly higher odds to have newly diagnosed diabetes mellitus (non-obese people with normal ALT, 1.7% as reference; ALT ≤ 40 U/L: 4.7%, OR 1.73, 95% CI 1.08-2.77, P = 0.023; ALT 41-80 U/L: 6.8%, OR 2.06, 95% CI 1.20-3.55, P = 0.009; ALT 81-120 U/L: 10.6%, OR 3.00, 95% CI 1.88-4.78, P < 0.001; ALT > 120 U/L: 17.0%, OR 5.68, 95% CI 3.03-10.7, P < 0.001).

However, with further adjustment for metabolic syndrome and viral hepatitis history, elevated ALT per se was not consistently associated with diabetes mellitus (ALT 41-80 U/L: OR 1.12, 95% CI 0.82-1.53; ALT 81-120 U/L: OR 1.69, 95% CI 0.98-2.90; ALT > 120 U/L: OR 2.76, 95% CI 1.35-5.65) and newly diagnosed diabetes mellitus (ALT 41-80 U/L: OR 1.13, 95% CI 0.79-1.62; ALT 81-120 U/L: OR 1.88, 95% CI 1.04-3.39; ALT > 120 U/L: OR 3.10, 95% CI 1.44-6.68).

As shown in Fig. 1, with further adjustment for BMI, high blood pressure, high serum triglyceride, low HDL-C and viral hepatitis history, obese people with elevated ALT had significantly higher odds to have newly diagnosed diabetes mellitus (non-obese people with normal ALT, 1.7% as reference; ALT ≤ 40 U/L: 4.7%, OR 1.73, 95% CI 1.08-2.77, P = 0.023; ALT 41-80 U/L: 6.8%, OR 2.06, 95% CI 1.20-3.55, P = 0.009;
Elevated ALT in obese uncovers new DM

In addition, ALT as a gluconeogenic enzyme, its gene transcription may be suppressed by insulin. Elevated ALT may result from an impairment in insulin signaling rather than a purely hepatocytic injury [24]. It can explain that a persistent elevated ALT may occur without recognized histological changes in the liver [25, 26]. Taking all these factors together, it seems logical to regard a sustained elevated ALT as an indicator of insulin resistance. However, elevated ALT may have various causes [27-29]. It may derive from increased hepatocytic injury, increased intrahepatocytic production or both. It may be particularly challenging to interpret in communities or countries with high prevalence of viral hepatitis.

In this study and our previous observation, elevated ALT was not consistently associated with diabetes mellitus [19]. This may give explanation to the controversy among different studies about the association between ALT values and diabetes mellitus [12-15, 17-19, 30]. Therefore, a coexisting insulin resistance-related metabolic syndrome feature may validate the accuracy of elevated ALT in reflecting underlying insulin resistance. In this study, we found that people with abdominal obesity have high odds for newly diagnosed diabetes mellitus especially when they had a concomitantly elevated ALT.

This study was limited by lack of comparison between ALT and other liver function tests (i.e. AST and GGT), and deficiency of nonpartisan recruitment with man predominant subpopulation sample and relatively younger age. Moreover, the ALT measurement was not repeated to confirm its persistence. However, this study still provides useful information.

Discussion

Metabolic syndrome is a syndrome which reflects underlying insulin resistance, and an indicator to adopt a healthier life style or even take early medical intervention to prevent the development of diabetes mellitus [10]. However, the high prevalence as 29% seen in our studied group and 30-40% in USA [6] and diverse features may make people reluctant to take it as a warning. Therefore, further analysis of individual metabolic syndrome features to screen out people with highest odds to develop diabetes mellitus may offer significant advantages. In this study, we found that a combination of elevated ALT and abdominal obesity had significant effects on the odds for incidence of newly diagnosed diabetes mellitus.

People with type 2 diabetes mellitus or high body fat have a higher prevalence of elevated ALT levels [21]. ALT has long been explored for its association with hepatic insulin resistance or whole body insulin resistance. The liver helps counter-regulation by glycogenolysis and gluconeogenesis. Insulin acts on liver to maintain euglycemia via suppression of hepatic glucose production and stimulation of glycogen synthesis. As an insulin sensitive organ, abnormalities of triglycerides storage and lipolysis in liver may precede hyperglycemia in people with insulin resistance. In animal studies, chronic hyperinsulinemia per se may induce hepatic insulin resistance, through a down-regulation of the insulin receptor substrate-2-mediated insulin signaling pathway. Meanwhile, an up-regulation of sterol regulatory element-binding protein 1c (SREBP-1c) occurs, leading to an increased intrahepatic lipogenesis [22]. This fatty change may further blunt insulin sensitivity and result in hepatocytic injury [23].

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**Conflict of Interest**

There was no conflict of interest reported.

**References**

Elevated alanine aminotransferase is associated with metabolic syndrome but not consistently associated with impaired fasting glucose or type 2 diabetes mellitus. *Diabetes Res Clin Pract* 94(1): 64-70.


