Increased alanine aminotransferase level and future risk of type 2 diabetes and impaired fasting glucose among the employees in a university hospital in Thailand

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Original article

Abstract

Aim. – The purpose of this study was to determine the association between baseline alanine aminotransferase (ALT) levels, and future risk of impaired fasting glucose and type 2 diabetes among the employees of a university hospital in Bangkok, Thailand.

Methods. – Totally, 2370 and 1619 workers without diabetes and impaired fasting glucose (IFG) at baseline, respectively, who were 35 years or older were followed during 2001–2005. Diagnosis of IFG and type 2 diabetes was based on the fasting plasma glucose levels of 100–125 and greater or equal to 126 mg/dl, respectively.

Results. – Higher baseline ALT levels were associated with future diabetes risk in an obvious dose-response manner (the OR [95% CI] for the groups with baseline ALT of 17–22, 23–38, and greater than 38 mg/dl comparing to the group with baseline ALT of 1–16 mg/dl were 4.75 [1.25–18.10], 6.14 [1.54–24.45], and 7.19 [1.32–39.16], respectively). Magnitude of association were even higher among those with existing IFG at baseline. The association patterns were consistent for both genders. Concerning the IFG risk, while those who developed IFG had significantly higher baseline ALT levels than those who remained normal at the end of follow-up period, further analyses did not show that baseline ALT was significantly associated with future IFG risk.

Conclusion. – Present study provided supporting evidence from a cohort of Asian subjects about the ALT and future type 2 diabetes risk.

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Résumé

Augmentation de l’alanine-aminotransférase et risque de développer un diabète de type 2 ou une hyperglycémie modérée à jeun chez des employés d’un centre hospitalier universitaire thaïlandais.

Objectif. – La présente étude avait pour but de déterminer l’association entre l’alanine-aminotransférase (ALAT) à l’inclusion et le risque ultérieur d’hyperglycémie modérée à jeun et de diabète de type 2 chez des employés d’un centre hospitalier universitaire de Bangkok, Thaïlande.

Méthodes. – Au total, 2370 sujets non diabétiques et 1119 sujets sans hyperglycémie modérée à jeun à l’inclusion âgés de plus de 35 ans ont été suivis de 2001 à 2005. Le diagnostic d’hyperglycémie modérée à jeun et celui de diabète de type 2 a été porté pour des glycémies à jeun respectivement de 100 à 125 et supérieure ou égale à 126 mg/dl.

Résultats. – Une élévation de l’ALAT à l’inclusion était associée dans les deux sexes à une augmentation du risque ultérieur de diabète, comme en témoignent l’augmentation croissante des rapports de cote (OR [95% IC]) (4,75 [1.25–18.10], 6,14 [1.54–24.45], et 7,19 [1.32–39.16]) en fonction des quartiles de l’ALAT à l’inclusion (17 à 22, 23 à 38, et supérieures à 38 mg/dl), par rapport au groupe dont l’ALAT à l’inclusion était comprise entre 1 et 16 mg/dl. L’amplitude de cette association était encore plus nette chez les sujets qui présentaient une hyperglycémie modérée à jeun à l’inclusion. En revanche, et bien que les sujets développant ultérieurement une hyperglycémie modérée à jeun aient des taux d’ALAT à l’inclusion...
plus élevés que ceux des patients restés normoglycémiques, une analyse complémentaire a montré qu’il n’y avait pas d’association entre l’ALAT à l’inclusion et le risque ultérieur d’hyperglycémie modérée à jeun.

Conclusion: – Cette étude permet de conclure, dans cette cohorte d’employés d’un hôpital thaïlandais, à l’association entre l’élévation de l’ALAT et le risque ultérieur de diabète de type 2.

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Keywords: ALT; AST; Type 2 diabetes; Impaired fasting glucose; Diabetes risk; Longitudinal study; Prognostic value

Mots clés : ALAT ; ASAT ; Diabète de type 2 ; Hyperglycémie modérée à jeun ; Risque de diabète ; Étude longitudinale

1. Introduction

Growing evidence suggested the possible association between abnormal hepatocellular functions, and type 2 diabetes. Prospective studies have found that high levels of hepatic enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltranspeptidase (GGT) are associated with the later development of diabetes [1–10]. These enzymes — particularly the ALT — are the common markers of a syndrome called nonalcoholic fatty liver disease (NAFLD), which is related to hepatic resistance, and increased hepatic glucose output [11]. Since the measurements of these enzymes are well standardized, and routinely available in laboratories, some researchers have suggested that they could be included in future diabetes prediction algorithms [8].

However, the association patterns between these enzymes, and type 2 diabetes are complex and not consistent across different studies [5,12]. Some researchers claimed that these discrepancies might have been due to the ethnic difference among the study populations [3]. Until now, only two studies investigated the association of hepatic enzymes, and type 2 diabetes among Asian populations. These included studies in Japanese and Korean workers with conflicting results about the association between raised ALT and future diabetes risks [6,7].

We thus have the opportunity to conduct study to investigate such associations among Thai workers which is another Asian population. Our specific aim was to determine association between the raised ALT, AST, and alkaline phosphatase (ALP), and future development of type 2 diabetes and impaired fasting glucose (IFG) among the employees in a university hospital in Bangkok, Thailand.

2. Research design and methods

2.1. Study population

The university hospital contained 1200 beds and employed totally 5000 workers in 2001. As the fasting plasma glucose was offered for every worker who was 35 years of age or older on annual basis, the target population for the study were those who were 35 years or older, and had participated in the annual physical checkup at least twice during years 2001–2005.

2.2. Survey procedure

Personal demographic data (such as gender, date of birth, educational level) was obtained from the computerized database of the hospital. Additional information about individual’s personal and family history of disease, cigarette smoking and alcoholic consumption was obtained by a questionnaire survey which was conducted once in 2003.

Annual health examination was conducted during 2001–2005. Four hundreds and ninety four (17.4%), 1307 (46.0%), 371 (13.1%), 459 (16.1%), and 159 (5.6%) were first examined consecutively during this period (totally 2790 workers). After an overnight fast, the participants underwent the anthropometric measurements and blood samples. Weight, height, and blood pressure (in the sitting position) were measured by staff nurses. Fasting plasma glucose (FPG), serum total cholesterol, triglycerides, uric acid, blood urea nitrogen (BUN), creatinine (Cr), alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase were measured in a standardized manner at the biomedical laboratory of the hospital. Similar procedures were utilized in the follow-up examinations.

2.3. Follow-up

In the study of type 2 diabetes incidence rate, participants without type 2 diabetes at baseline were followed until having the disease or until the last available annual examination result for those who did not develop the disease during the follow-up period (2002–2005). In the determination of IFG incidence rate, only participants without type 2 diabetes or IFG at baseline were included. They were then followed until having IFG or until the last available examination year for those who have not developed IFG. Workers who developed type 2 diabetes directly from normal FPG at baseline were not included in the IFG incidence study.

2.4. Definitions

Diagnosis of diabetes was defined according to the American Diabetic Association (ADA) criteria, i.e. when FPG level was greater or equal to 126 mg/dl (7.0 mmol/l) or having history of physician diagnosed of diabetes or those who were on treatment. Impaired fasting glucose or prediabetes was defined as those with FPG levels greater or equal to 100 mg/dl (5.6 mmol/l) but less than 126 mg/dl (7.0 mmol/l) [13].

Body mass index (BMI) was calculated as (weight in kg)/(height in meters)^2. Physical status of individuals was classified based on the BMI as:

- underweight for BMI less than 18.5 kg/m^2;
Blood pressure was classified according to the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC-7) [15]. Total serum cholesterol and triglyceride levels were categorized according to the third report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (ATP III) [16]. Serum AST, ALT, and ALP were classified into normal or high by using the cut-points of 38, 38, and 117 mg/dl respectively, for these biochemical parameters. In addition, the normal ranges of these parameters were further categorized into quartile to facilitate detailed examination about the associations between these parameters and abnormal plasma glucose levels.

2.5. Statistical analysis

Study subjects were classified into “Normal”, “IFG”, or “Diabetes” groups according to the FPG status at the end of the follow-up period. In the comparison among these groups, means (standard deviation [S.D.]) or medians (interquartile ranges), were calculated for continuous variables with normal or skewed distributions respectively, and proportions (S.D.) were calculated for categorical variables. Skew data were log transformed and ANOVA was then used to assess the significant difference among groups [17]. Test for trend among these FPG groups was also conducted by using Kruskal–Wallis test. Crude and adjusted associations between the incidence IFG or type 2 diabetes (dependent variables) and hepatic enzyme statuses (independent variables) were then investigated by the logistic regression analyses [18]. Analyses for the incidence IFG and type 2 diabetes groups were conducted separately among subjects without such condition at baseline. In Table 2, tests for trend were carried out fitting AST and ALT in their ordinal form. The P-value of less than 0.05 was the cut-off for the statistically significant level.

3. Results

3.1. Subject Characteristics

Of all 3243 workers who were 35–60 years old and eligible for the annual fasting glucose examination during 2001–2005, 2790 (86.0%) participated in such examination at least once. Detailed analysis showed that while the non-participants contained higher proportion of male workers (29.0% versus 19.7%) with higher educational level (53.1% versus 50.5% for those with 13+ years of education), they were quite similar to the participants according to age and work duration. The mean age (S.D.) was 42.7 (7.6) years old and the average working duration (S.D.) was 18.1 (7.7) years.

Of all 2790 workers participated in the annual fasting glucose examination at least once during 2001–2005, 344 (12.3%) and 105 (3.8%) workers had IFG and type 2 diabetes respectively, at baseline. Of 2685 workers without type 2 diabetes at baseline, 2370 workers (88.3%) participated 2+ annual examination years and were included in this study. The remaining 315 non-participants were slightly younger and had lower baseline FPG level than the participants (means age were 42.0 and 44.2 years, with P < 0.05; means baseline FPG levels were 86.3 and 89.8 mg/dl, with P < 0.05 respectively, for non-participant and participant groups). However, their baseline BMI levels were comparable (means baseline BMI were 23.6 and 23.7, with P > 0.05 respectively, for non-participant and participant groups).

Of all 2370 workers without type 2 diabetes at baseline, 2050 (86%) and 320 (14%) had normal FPG and IFG at baseline respectively. The follow-up periods were 1–4 years, with the mean ± S.D. of 2.60 ± 0.97 years. Among 2050 workers with normal FPG at baseline, 1962 (96%) workers still had normal FPG, while 73 (4%) and 15 (1%) workers developed IFG and type 2 diabetes respectively. For those 320 workers with IFG at baseline, 197 (62%) turned to normal FPG, while 90 (28%) workers still had IFG and 33 (10%) workers developed type 2 diabetes. All diabetes cases were diagnosed basing on the annual FPG results during the follow-up period.

Comparison among the “normal”, “IFG”, and “diabetes” groups showed that baseline age and BMI were significantly higher among the IFG and diabetes groups than the normal group (Table 1). Trends of increase for these parameters from the normal to the IFG and the diabetes groups were also obvious. Almost all baseline biochemical parameters including FPG, AST, ALT, and ALP levels also showed the prominent stepwise increases among these groups. However, the AST-to-ALT ratio showed an inverse trend. Follow-up times were also significantly shorter across these three groups.

Stepwise decrease in the proportion of female gender for the normal, IFG, and diabetes groups was also demonstrated. There was, however, no difference in the frequency of cigarette smoking, alcohol consumption, family history of diabetes, and educational level of six years or less among these groups.

3.2. Hepatic enzyme levels

Fig. 1 demonstrated the age-standardized values of baseline AST and ALT levels among the three groups for both genders. Overall, baseline AST and ALT levels in the groups of men workers were significantly higher than those levels in the corresponding subgroups of women workers. Baseline AST and ALT levels in the IFG and diabetes groups were significantly higher than those in the normal group for both genders. However, while the ALT levels showed pronounce stepwise increase pattern across groups, the AST levels did not show such pattern. The pattern of relative levels of baseline AST and ALT were consistent for both genders.

When stratifying the workers into those with and without IFG at baseline, the stepwise increase in baseline ALT levels across the disease groups were more pronounce for workers with IFG at baseline but obscure for those with normal FPG at baseline.
Table 1
Baseline clinical and metabolic parameters according to plasma glucose levels

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Disease status at the end of follow-up</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal n = 2159</td>
<td>IFG n = 163</td>
</tr>
<tr>
<td>Age (years)(^a)</td>
<td>Mean ± S.D.</td>
<td>Mean ± S.D.</td>
</tr>
<tr>
<td>Follow-up time (years)</td>
<td>43 ± 11</td>
<td>47 ± 10(^b)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>23.4 ± 0.1</td>
<td>26.0 ± 0.4(^b)</td>
</tr>
<tr>
<td>AST (units/L)(^a)</td>
<td>20.0 ± 7.0</td>
<td>22.0 ± 9.0(^b)</td>
</tr>
<tr>
<td>ALT (units/L)(^a)</td>
<td>16.0 ± 11.0</td>
<td>22.0 ± 23.0(^b)</td>
</tr>
<tr>
<td>AST-to-ALT ratio(^a)</td>
<td>1.2 ± 0.5</td>
<td>1.0 ± 0.4</td>
</tr>
<tr>
<td>ALP (units/L)(^a)</td>
<td>63.0 ± 24.0</td>
<td>71.0 ± 29.0(^b)</td>
</tr>
</tbody>
</table>

Mean (S.D.) baseline ALT levels for male workers with IFG at baseline who were normal, IFG, and diabetes at follow-up were 39.8 (1.7), 47.7 (2.4), and 50.5 (3.8) mg/dl respectively, while those levels for male workers with normal FPG at baseline who were normal, IFG, and diabetes at follow-up were 33.6 (1.1), 40.5 (2.7), and 37.3 (5.6) mg/dl respectively. In similar pattern, mean (S.D.) baseline ALT levels for female workers with IFG at baseline who were normal, IFG, and diabetes at follow-up were 24.2 (1.6), 32.1 (2.3), and 34.8 (3.8) mg/dl respectively, while those levels for female workers with normal FPG at baseline who were normal, IFG, and diabetes at follow-up were 17.9 (0.5), 24.8 (2.6), and 21.7 (5.5) mg/dl respectively (data not shown).

Age-standardized ALP and AST-to-ALT ratio for the normal, IFG, and diabetes groups were not statistically significantly different. Changes in these hepatic enzyme levels over the follow-up

![Enzyme level (mg/dl)](Image)

Fig. 1. Baselines hepatic enzyme levels (age adjusted) according to gender and disease status at the end of follow-up period.
Table 2
Logistic regression analysis results for the baseline hepatic enzyme level and the risk of abnormal FPG

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>IFG</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
<td>Adjusted (Model I)</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Baseline AST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1 unit increase</td>
<td>1.02 (1.01–1.04)</td>
<td>1.02 (1.00–1.04)</td>
</tr>
<tr>
<td>Quartile 1 (1–12 mg/dl)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Quartile 2 (13–16 mg/dl)</td>
<td>1.04 (0.58–1.87)</td>
<td>0.87 (0.47–1.61)</td>
</tr>
<tr>
<td>Quartile 3 (17–22 mg/dl)</td>
<td>1.46 (0.82–2.60)</td>
<td>1.09 (0.58–2.05)</td>
</tr>
<tr>
<td>Quartile 4 (23–38 mg/dl)</td>
<td>1.33 (0.76–2.34)</td>
<td>0.75 (0.39–1.44)</td>
</tr>
<tr>
<td>High (&gt; 38 mg/dl)</td>
<td>1.93 (0.79–4.73)</td>
<td>1.10 (0.40–3.03)</td>
</tr>
<tr>
<td>Trend</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Baseline ALT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1 unit increase</td>
<td>1.01 (1.01–1.02)</td>
<td>1.00 (1.00–1.02)</td>
</tr>
<tr>
<td>Quartile 1–2 (1–16 mg/dl)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Quartile 3 (17–22 mg/dl)</td>
<td>1.29 (0.78–2.13)</td>
<td>1.09 (0.63–1.89)</td>
</tr>
<tr>
<td>Quartile 4 (23–38 mg/dl)</td>
<td>1.62 (1.00–2.64)</td>
<td>1.02 (0.58–1.80)</td>
</tr>
<tr>
<td>High (&gt; 38 mg/dl)</td>
<td>2.13 (1.14–3.98)</td>
<td>1.20 (0.57–2.53)</td>
</tr>
<tr>
<td>Trend</td>
<td>P &lt; 0.01</td>
<td>NS</td>
</tr>
</tbody>
</table>

Model I: adjusted for gender, education, alcohol consumption, cigarette smoking, family history of diabetes, age at start, baseline values of BMI, systolic blood pressure, diastolic blood pressure, serum cholesterol, triglyceride, fasting plasma glucose, blood urea nitrogen and uric acid, and follow-up time.
Model II: adjusted for variables in Model I plus AST (or ALT) for the OR determination of ALT (or AST).
NS: not statistically significant.
* P < 0.05.
a Combine because no diabetes case in the lowest quartile.
period among these three groups did not show any consistent pattern (results not shown).

3.3. Hepatic enzyme levels and future risk of abnormal FPG

Univariable analyses showed that higher levels of both AST and ALT associated with type 2 diabetes risk in the pronounced dose-response manner, particularly for the higher-than-normal subgroups (Table 2). However, after controlling for potential confounding effects of various factors (gender, education, alcohol consumption, cigarette smoking, family history of diabetes, age at start, baseline values of BMI, systolic blood pressure, diastolic blood pressure, serum cholesterol, triglyceride, fasting plasma glucose, blood urea nitrogen, uric acid, and follow-up time; model I), only the higher levels of ALT were still significantly associated with the diabetes risk. When mutually controlling for each other confounding effect between AST and ALT (model II), the magnitude of associations between the baseline ALT levels and the diabetes risk were stronger and their dose-response pattern remained. The baseline ALT level was no longer the significant predictor of future diabetes risk.

When restricting the subjects to only those workers with IFG at baseline (320 workers) and reexamined the baseline ALT and diabetes risk, their magnitudes of association were tremendously stronger. The odds ratios (95% CI) for the groups with baseline ALT of 13–16, 17–22, 23–38, and greater than 38 mg/dl compared to the group with baseline ALT of 1–12 mg/dl were 55.35 (1.40–2188.49), 172.18 (4.27–6939), and 84.02 (1.70–4156.5) respectively (results not shown).

Concerning the IFG risk, baseline ALT level also seemed to be related to future IFG risk but not as obvious or statistically significant (Table 2).

4. Discussion

In present study, we demonstrated the possible association between baseline ALT level and future development of type 2 diabetes among a predominantly female employee group in Thailand. Higher baseline ALT associated with future diabetes risk in an obvious dose-response manner (the odds ratios [95% CI] for the groups with baseline ALT of 17–22, 23–38, and greater than 38 mg/dl comparing to the group with baseline ALT of 1–12 mg/dl were 4.75 [1.25–18.10], 6.14 [1.54–24.45], and 7.19 [1.32–39.16] respectively).

Our reported association between baseline ALT and future type 2 diabetes risk was consistency with recent report of the West of Scotland Coronary Prevention Study (WOSCOPS) by Sattar et al. and those reported by other investigators previously [1–8]. We further demonstrated that the association between baseline ALT and future diabetes risk was more obvious in those with existing IFG at baseline. The association pattern was similar for both men and women. This was in contrast to those data reported by André et al. in the data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR study), who reported the association between baseline ALT and future diabetes risk in men only [4]. They also reported that ALT was no longer significantly associated with type 2 diabetes when gamma-glutamyltransferase (γGT) activity was taking into account. Since our investigation did not include γGT, we were thus unable to control for its potentially confounded effect in our analyses.

Concerning the IFG risk, we found that those who developed IFG had significantly higher baseline ALT levels than those who remained normal at the end of follow-up period. However, further analyses did not show that baseline ALT was significantly associated with future IFG risk. This might be due to our sample size was too small to examine this association. Another explanation might be that the manifestation of hepatic abnormality as the harbinger of diabetes is slow during the early period of abnormal glucose metabolism, but accelerated during the later period, particularly after the period of IFG development. Cugati et al. recently reported that a number of type 2 diabetes predictors also predict future IFG risk in the older Australian [19]. They however did not include liver enzymes in their investigation. So, the issue of whether baseline ALT level is a predictor of future IFG risk needed to be confirmed in future investigation.

Some limitations needed to be mentioned in our study. Approximately, 11.7 and 30.9% of eligible subjects were lost follow-up. However, detailed investigation showed that participant and non-participant groups were quite comparable according to age, baseline BMI and FBS levels, gender composition and proportion of individuals with family history of diabetes.

While previous studies reported the association between family history of diabetes and future type 2 diabetes risk, our study result did not demonstrate such association. This might be due to the confusion of responsible question items in our data collecting instrument. Confounded effect by family history of diabetes thus might not be adequately controlled in our analyses. However, our reported magnitudes of association between baseline ALT and future diabetes risk, as well as their consistent dose-response patterns, showed that its biased effect should not be so serious.

In conclusion, our study confirmed the premise that baseline ALT significantly predict future type 2 diabetes risk in both female and male hospital employees in Bangkok, Thailand. Its predictive power seemed to be stronger among those with existing IFG at baseline.

Acknowledgement

This project was supported by Chulalongkorn Memorial Hospital and Chulalongkorn University.

References


