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LETTER TO THE EDITOR

# Optimal cut-off value of alanine aminotransferase level to precisely estimate the presence of fatty liver in patients with poorly controlled type 2 diabetes

Non-alcoholic fatty liver disease is associated with an increased risk of liver cirrhosis and cardiovascular events[1]. In non-diabetic subjects, the serum level of alanine aminotransferase (ALT) is correlated with liver fat accumulation[2], and its upper limit of the normal range is considered to be 40 IU/mL[3]. However, a recent study has suggested that the true upper limit is lower than 40 IU/mL[4]. In addition, it remains unknown what is an optimal cut-off value of ALT level to precisely estimate the presence of fatty liver in patients with poorly controlled type 2 diabetes, which could induce some adverse effect (glucose toxicity) on the liver.

We recruited 315 Japanese patients with poorly controlled type 2 diabetes (glycated hemoglobin ≥8.4%) who visited Ako Central Hospital, Ako, Japan, from 2004 to 2014. Patients' characteristics were as follows: men 63%; age 58 ± 14 years (mean ± standard deviation); body mass index 25.6 ± 6.0 kg/m$^2$; duration of diabetes 8.5 ± 6.9 years; glycated hemoglobin 9.9 ± 2.0%; fasting plasma glucose 86 ± 59 mg/dL; fasting insulin 7.4 ± 5.6 μg/mL; homeostatic model assessment of insulin resistance 3.4 ± 2.5; homeostatic model assessment of β-cell function 31.7 ± 41.1; ALT 29.7 ± 23.1 U/L; aspartate aminotransferase 23.6 ± 15.0 U/L; γ-glutamyltranspeptitase 70.8 ± 119.6 U/L; platelet count 24.4 ± 6.8 × 10$^4$/μL; and the ratio of liver computed tomography value/spleen computed tomography value (L/S ratio) 1.11 ± 0.27. A total of 80 patients (25%) had fatty liver, which was diagnosed by established radiologists using abdominal computed tomography scan. Among them, 138 patients were drug naïve, 177 were oral hypoglycemic agent users and there were no insulin users (we excluded insulin users in the present study). Non-parametric data were analyzed by Wilcoxon signed–rank test. $P < 0.05$ was regarded as statistically significant. The study protocol was approved by the hospital ethics committee.

To evaluate the relationship of the variables to fatty liver, we carried out multiple logistic regression analysis in which fatty liver taken as a dependent variable, and age, sex, ALT level and L/S ratio as predictor variables. It is noted here that we ruled out multicollinearlity between ALT and the L/S ratio; a correlation coefficient of ALT and L/S ratio was –0.45 ($P < 0.0001$), and the absolute value of a correlation coefficient (0.45) was lower than 0.9. This analysis showed that ALT level and L/S ratio were independent factors contributing to the development of fatty liver (ALT: partial correlation coefficient 0.024; $P = 0.001$; odds ratio 1.024; 95% confidence interval 1.01–1.039; L/S ratio: partial correlation coefficient –3.44; $P < 0.001$; odds ratio 0.032; 95% confidence interval 0.009–0.12). ALT levels in patients with fatty liver were significantly higher compared with those without it (Table 1). Furthermore, in receiver operating characteristic analysis, the optimal cut-off value of ALT level to precisely estimate the presence of fatty liver was 28.0 U/L, which was much lower compared with the generally recognized upper limit of normal range (40.0 U/L). In addition, there was a sex difference in the optimal cut-off value of ALT level (male ALT 28 U/L, female ALT 20 U/L). The L/S ratio in patients with fatty liver was significantly lower compared with those without it. In contrast, there was no significant difference in platelet count between patients with and without fatty liver (Table 1).

Our present study showed that elevated ALT level and low L/S ratio were independently related to fatty liver. Furthermore, we showed that the optimal cut-off value of ALT level to precisely estimate the presence of fatty liver was as low as 28.0 U/L. We assume that some adverse effects induced by hyperglycemia (glucose toxicity) influenced such an optimal value of ALT level.

There was a limitation to the present study. As we did not have data for well-controlled diabetic patients or non-diabetic subjects, we failed to directly compare the optimal cut-off value to estimate the presence of fatty liver using receiver operating characteristic analysis between poorly controlled type 2 diabetic patients and well-controlled diabetic patients or non-diabetic participants. However, to address this point, we further analyzed the data of the participants ($n = 33$), which we followed for over 6 months after the initiation of the treatment. As the results, glycated hemoglobin levels were significantly decreased from a median of 9.8% (interquartile range 10.7–9.2; at the first visit) to a median of

*Corresponding author. Hideaki Kaneto
Tel.: +81-86-462-1111
Fax: +81-86-464-1046
E-mail address: kaneto@med.kawasaki-m.ac.jp
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**Table 1** | Optimal cut-off value of alanine aminotransferase level and ratio of liver computed tomography value/spleen computed tomography value to precisely estimate the presence of fatty liver in patients with poorly controlled type 2 diabetes

| | Fatty liver (+) | | Fatty liver (–) | | *P*-value | ROC analysis | |
|---|---|---|---|---|---|---|---|
| | *n* | Median (IQR) | *n* | Median (IQR) | | AUC | Cut-off value |
| ALT (U/L) | | | | | | | |
| All | 80 | 38 (23–55) | 235 | 18 (14–29) | <0.0001 | 0.785 | 28 |
| Male | 45 | 36 (23–55) | 155 | 19 (14–30) | <0.0001 | 0.778 | 28 |
| Female | 35 | 40 (23–56) | 80 | 18 (12–29) | <0.0001 | 0.786 | 20 |
| L/S ratio | | | | | | | |
| All | 80 | 0.91 (0.79–1.07) | 235 | 1.21 (1.10–1.31) | <0.0001 | 0.834 | 1.05 |
| Male | 45 | 0.90 (0.80–1.10) | 155 | 1.20 (1.08–1.30) | <0.0001 | 0.815 | 1.07 |
| Female | 35 | 0.94 (0.80–1.05) | 80 | 1.20 (1.13–1.30) | <0.0001 | 0.837 | 1.05 |
| Platelet ($\times 10^4/\mu L$) | | | | | | | |
| All | 80 | 23 (18–27) | 235 | 23 (20–28) | 0.306 | 0.538 | ND |
| Male | 45 | 24 (19–27) | 155 | 23 (19–28) | 0.816 | 0.489 | ND |
| Female | 35 | 23 (18–27) | 80 | 24 (22–29) | 1.000 | 0.597 | ND |

Comparison between two groups was carried out by Wilcoxon's rank–sum test. ALT, alanine aminotransferase; AUC, area under the curve; IQR, interquartile range; L/S ratio, ratio of liver computed tomography value/spleen computed tomography value; ND, not detected; ROC, receiver operating characteristic curve.

6.7% (interquartile range 7.3–5.8; 6 months after the first visit; $P < 0.0001$, Wilcoxon's signed–rank test). As glycemic control was ameliorated, ALT levels were also significantly decreased from a median of 56 U/L (interquartile range 77–43; at the first visit) to a median of 23 U/L (interquartile range 36–16; 6 months after the first visit; $P < 0.0001$, Wilcoxon's signed–rank test). These results suggest that ALT cut-off level could be altered by the glycemic control although further analysis would be necessary to conclude this point.

Taken together, we should consider the possibility of fatty liver even when the ALT level is within the normal range in patients with poorly controlled type 2 diabetes.

## DISCLOSURE

The authors declare no conflict of interest.

Akihito Tanabe[1,2], Fuminori Tatsumi[1,2], Seizo Okauchi[2], Hiroki Yabe[1], Tomohiro Tsuda[1], Kazuma Okutani[3], Kazuki Yamashita[4], Koji Nakashima[1,2], Kohei Kaku[5], Hideaki Kaneto[2]*

*Departments of [1]Internal Medicine, [3]Laboratory, and [4]Exercise Therapy, Ako Central Hospital, Ako, Divisions of [2]Diabetes, Endocrinology and Metabolism, and [5]General Internal Medicine, Kawasaki Medical School, Kurashiki, Japan*

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