Increased brain-derived neurotrophic factor in the serum of persons with nonalcoholic fatty liver disease

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Abstract. The increasing prevalence of nonalcoholic fatty liver disease (NAFLD) is a global health problem. In recent years, the inhibitory effect of brain-derived neurotrophic factor (BDNF) on diabetes mellitus and fatty liver has been clarified. The purpose of this study was to analyze the relationship between serum BDNF and NAFLD which caused by abnormal metabolism of glucose and lipids. This cross-sectional study involved 429 participants (mean age, 63.5 years; men, 38.5%) with low alcohol intake. Of the participants, those who had an increase in echogenicity of the liver parenchyma and hepato-renal contrast on ultrasonography were classified as the NAFLD group (n = 88), and the others were classified as the normal (n = 341) group. The NAFLD group was further classified into a mild group (n = 60) and a severe group (n = 28) based on the intensity of echogenicity and visualization of the hepatic vessels and diaphragm. Median BDNF levels were higher in the NAFLD group than the normal group (35.5 vs. 42.3 ng/mL, p < 0.01). Furthermore, BDNF levels tended to be associated with the severity of NAFLD (p < 0.01). In addition to the univariate analysis, in the sex- and age-adjusted model, there was a significant association between the BDNF levels and NAFLD severity (p < 0.01). The fully adjusted regression analysis also showed a positive association between the serum BDNF level and NAFLD (p < 0.01). These results suggest that NAFLD patients have a compensatory increase in circulating BDNF levels.

Key words: Nonalcoholic fatty liver disease, Brain-derived neurotrophic factor, Cross-sectional study, Japanese population

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) is a general term for fatty liver excluding alcoholic, viral and drug-induced fatty liver disease. NAFLD often develops in individuals with obesity, type 2 diabetes mellitus (T2DM), and hyperlipidemia, and is considered to be a liver disorder attributable to metabolic syndrome [1, 2]. Histologically, NAFLD is divided into nonalcoholic fatty liver (NAFL) and nonalcoholic steato-hepatitis (NASH) [3]. NASH includes inflammation and fibrosis in addition to simple fatty liver. Furthermore, the progression of NASH may lead to cirrhosis and hepatocellular carcinoma. In recent years, there has been an increase in the prevalence of NAFLD due to the increasing frequency of obesity worldwide, especially in developed countries, making this disease a global medical issue [4].

Brain-derived neurotrophic factor (BDNF), one of the neurotrophins, binds to and activates its cognate receptor, which is termed tyrosine receptor kinase B (TrkB). BDNF/TrkB initiates a signal transduction system that regulates physiological activities such as neuronal cell development, growth, maintenance, and regeneration.
Previous studies reported that an increase in BDNF in the dentate gyrus and perirhinal cortex of mice improves recognition memory, whereas a decrease in BDNF impairs memory and learning ability [7-9]. A clinical study of depressed patients also reported that these patients have decreased serum BDNF levels [10]. BDNF is detected primarily in the cerebrum and hippocampus, but BDNF is expressed ubiquitously and has been shown to be present in blood [11]. Most BDNF in the blood is present in a form bound to platelets. The quantity of BDNF produced by the platelets themselves is very small; instead, it appears that platelets transport BDNF derived from other organs [12]. This result suggests that circulating BDNF levels may vary depending on physiological and pathological conditions.

Given the abundant expression of BDNF in the cerebrum and hippocampus and the neurotrophic role of this protein, previous studies have focused primarily on the action of BDNF in the nervous system. However, in recent years, there has been an increasing number of reports that BDNF is also involved in energy metabolism. For example, administration of BDNF to diabetic mice improves glucose metabolism [13]. Clinical studies have shown that serum BDNF levels are lower in patients with T2DM and heart failure than in healthy individuals [14-16], and that obesity is associated with increased serum BDNF levels [17]. As the number of such reports has risen, the relationship between BDNF and lifestyle-related diseases (e.g., diabetes mellitus and metabolic syndrome) has attracted increasing attention.

Not surprisingly, given that NAFLD is caused by abnormal metabolism of glucose and lipids [18, 19], patients with NAFLD have been observed to show fluctuations in serum BDNF levels. However, few reports, to our knowledge, have focused on the relationship between NAFLD and serum BDNF concentrations at the population level. We hypothesized that exploration of the relationship between NAFLD and serum BDNF levels is likely to be informative. Therefore, a cross-sectional study was performed to clarify the relationship between NAFLD and serum BDNF levels in individuals being screened as part of their standard health examinations.

Materials and Methods

Study participants

A health examination has been conducted in the town of Yakumo, Hokkaido, Japan, every August since 1982. We have undertaken a field study (the Yakumo Study) using these health examinees. The present study was conducted as part of the Yakumo Study. Of the 525 people who underwent the general health examination in Yakumo, Hokkaido, Japan, in 2015, 429, excluding 88 who had alcohol intake exceeding the criterion and 8 who had missing test data, were finally recruited as subjects. All subjects provided written informed consent. The study protocol was approved by the Ethics Committee of Fujita Health University (Approval No. HM19-061) and complied with the guidelines of the Declaration of Helsinki and its subsequent amendments.

Participant data

The health status, drinking history, and smoking history of the participants were obtained via a self-completed questionnaire administered with the support of public health nurses at the health examination site. Based on each participant’s self-reported daily alcohol consumption (amount and type of alcoholic drink) determined from the questionnaire, the daily rate of ethanol intake was calculated. In this study, we excluded from our analysis men consuming ≥30 g ethanol/day and women consuming ≥20 g ethanol/day, the threshold values for the definition of NAFLD in the Japanese guideline, were excluded from the analysis [20]. Height, weight, waist circumference, and blood pressure were measured, and body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m).

Assessment of hepatic steatosis

Ultrasound examination was performed by any of three certified sonographers (Japan Society of Ultrasonics in Medicine) using a ProSound α7 with UST-9130 convex probe (Hitachi Aloka Medical, Tokyo, Japan). The presence of intrahepatic steatosis was assessed based on the results of ultrasound examination. Ultrasonography images were independently evaluated by each of the three sonographers and classified into three levels: normal, mild, and severe [20, 21]. Normal was defined as a state in which neither increased echogenicity of the liver parenchyma nor hepato-renal contrast were observed. Mild hepatic steatosis was defined as a slight increase in echogenicity and hepato-renal echo contrast. Severe hepatic steatosis was defined as a marked increase in liver echogenicity and poor visualization or a lack of visualization of the hepatic vessels and diaphragm. If there were disagreements regarding the classification among the sonographers, participants were classified based on the diagnosis shared by the majority (i.e., 2 of 3) of the evaluators.

Blood biochemistry

As part of the examinations, a fasting blood sample (no anti-coagulant) was collected from each participant. Following clotting, the samples were centrifuged, and the serum supernatants were collected within 1 hour after collection. The resulting serum samples were stored at
Statistical analysis

Statistical analyses were performed using JMP version 14.2.0 software (SAS Institute, Cary, NC, USA) and R version 3.5.0. Statistical analyses were performed with a two-tailed Student’s t-test; Wilcoxon rank sum test; Steel-Dwass test; Tukey-Kramer’s HSD test; 

Results

Table 1 shows the characteristics of 429 subjects with...
subthreshold alcohol intake sorted by NAFLD severity. A total of 341 participants (79.5%) were classified into the normal group, and 88 participants (20.5%) were classified into the NAFLD group. For the severity of fatty liver, 60 participants were categorized in the mild group (14.0% of the total, 68.2% of the NAFLD group) and 28 were categorized in the severe group (6.5% of the total, 31.8% of the NAFLD group). The results of blood chemistry analysis showed that HbA1c, albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), TG, and LDL-cholesterol were significantly higher in the mild group and in the severe group than in the normal group. BMI was also significantly higher in the mild group and in the severe group than in the normal group. There was no significant difference in the proportion of smokers between the normal group and the NAFLD group. Correlation analysis was performed to investigate the relationship between the BDNF level and metabolic parameters (Table 2). There were significant, but weak, negative correlations with age and AST. However, no significant correlations were found with other parameters. In addition, there was no difference in serum BDNF levels by sex.

The serum BDNF level was significantly higher in the NAFLD group than in the normal group ($p < 0.01$, Fig. 1A). In addition, the serum BDNF level was significantly higher in the mild group and the severe group than in the normal group (normal vs. mild: $p = 0.048$; normal vs. severe: $p = 0.021$; Fig. 1B). There was no significant difference in serum BDNF levels between the mild and severe groups. However, a trend test using the Jonckheere-Terpstra test showed that serum BDNF levels tended to increase as the severity of NAFLD increased ($p < 0.01$, Fig. 1B).

Ordinal logistic regression analysis was performed to identify confounding factors that might contribute to the elevation of serum BDNF levels in the NAFLD group (Table 3). Ordinal logistic regression analysis of the association between the serum BDNF level and the severity of NAFLD with adjustment for age and sex showed a significant correlation between the BDNF level and NAFLD severity ($p < 0.01$, Model 1). After additional adjustment for HbA1c, SBP, and smoking history to Model 1 to exclude the effects of diabetes mellitus, hypertension, and smoking history, the association between the serum BDNF level and NAFLD severity remained significant ($p < 0.01$, Model 2). Moreover,

**Table 2** Correlation analysis of BDNF with metabolic parameters

| Parameter          | $\rho$  | $p$-value |
|--------------------|--------|-----------|
| Age (y)            | -0.240 | <0.001    |
| BMI (kg/m$^2$)     | 0.081  | 0.094     |
| SBP (mmHg)         | 0.006  | 0.905     |
| Glucose (mg/dL)    | 0.060  | 0.216     |
| HbA1c (%)          | 0.019  | 0.695     |
| TG (mg/dL)         | 0.076  | 0.118     |
| AST (IU/L)         | -0.115 | 0.017     |
| ALT (IU/L)         | -0.021 | 0.666     |

Correlation analysis of BDNF with metabolic parameters. Spearman’s rank correlation coefficient was used for the statistical analysis.

BDNF, brain derived neurotrophic factor; NAFLD, nonalcoholic fatty liver disease

![Fig. 1](image)

**Fig. 1** Comparison of serum BDNF levels based on severity of NAFLD

(A) Comparison of serum BDNF levels between the two groups (Normal and NAFLD). Wilcoxon rank sum test was used for statistical analysis.

(B) Comparison of serum BDNF levels between the three groups (Normal, Mild, and Severe). Steel-Dwass test was used for statistical analysis (vs. Normal). The Jonckheere-Terpstra test was used for the trend test.

BDNF, brain derived neurotrophic factor; NAFLD, nonalcoholic fatty liver disease
BMI and TG were added to Model 2 to adjust for the effects of obesity and hyperlipidemia, which are closely associated with fatty liver (Model 3). This analysis also showed a significant association between the serum BDNF level and NAFLD severity \( (p < 0.01) \). These results showed that the higher serum BDNF level observed in the NAFLD group was an independent factor regardless of other confounding factors.

### Discussion

In this study, the association between the serum BDNF level and NAFLD status was examined. It was found that the serum BDNF concentration was significantly higher in the NAFLD group than in the normal group. Furthermore, it was found that the serum BDNF level tended to increase with the severity of NAFLD even after adjustment for confounding factors.

As described in the introduction, there are some reports that BDNF, which is a type of neurotrophin, is involved in glucose and lipid metabolism [13, 23-25]. Specifically, BDNF lowers blood glucose levels and improves glucose metabolism by increasing pancreatic insulin production [13, 23]. In addition, BDNF reduces body weight by increasing energy consumption, reduces blood lipids and liver weight, and has the action of enhancing lipid metabolism signals [24, 25]. These effects are triggered by a mechanism different from BDNF’s effects on the nervous system, such as loss of appetite [13]. Overall, BDNF is involved in peripheral tissue glucose and lipid metabolism and energy consumption, in addition to nerve growth and protection. It has also been suggested that the action of BDNF is observed throughout the body wherever TrkB receptors are expressed, such as in the liver, pancreas, and adipose tissue. Based on these findings, the present study focused on blood BDNF as a factor that reflects NAFLD pathology.

The present study showed that participants with NAFLD had higher serum BDNF levels than normal participants. To examine further the relationship between the severity of NAFLD and the serum BDNF level, the NAFLD patients were divided into mild and severe cases, and the serum BDNF levels were compared between these two NAFLD sub-groups. It was found that serum BDNF levels increased with the severity of NAFLD, as demonstrated via a trend test. Such differences in serum BDNF levels between the NAFLD sub-groups indicate the existence of compensatory changes for the manifestations of NAFLD. We postulate that, within the NAFLD group, the severity of NAFLD may be suppressed by a compensatory increase in serum BDNF, which counteracts abnormal glucose and lipid metabolism and exerts an inhibitory effect on lipid deposition in the liver. Consistent with our hypothesis a study of Italian women reported that serum BDNF levels were lower in anorexic patients, whereas serum BDNF levels were higher in obese individuals [17]. In anorexic patients, the decreased serum BDNF levels presumably would stimulate the appetite and suppress the metabolism of energy sources such as glucose and lipids; conversely, in obese individuals, increased serum BDNF levels would reduce appetite and promote decomposition of accumulated glucose and lipid [17].

Liu, et al. compared serum BDNF levels between pre-diabetic and diabetic groups and found that the pre-diabetic group had a higher serum BDNF than the diabetic group [14]. They also compared both these groups with the healthy population, and both the pre-diabetic and diabetic groups had significantly higher serum

| Variable | Model 1a | Model 2b | Model 3c |
|----------|----------|----------|----------|
|          | B       | p-value | B       | p-value | B       | p-value |
| BDNF     | 0.023   | <0.01   | 0.022   | <0.01   | 0.022   | <0.01   |
| Age      | -0.010  | 0.415   | -0.035  | 0.012   | -0.011  | 0.467   |
| Sex      | -0.461  | 0.060   | -0.428  | 0.164   | -0.217  | 0.515   |
| HbA1c    | 1.163   | <0.01   | 0.845   | <0.01   |         |         |
| SBP      | 0.026   | <0.01   | 0.015   | 0.037   |         |         |
| Smoking  | -0.167  | 0.587   | -0.098  | 0.772   |         |         |
| BMI      |         |         | 0.295   | <0.01   |         |         |
| TG       |         |         | 0.006   | <0.01   |         |         |
| \( R^2 \) | 0.039   | 0.159   | 0.290   |         |         |
BDNF levels in comparison. This result also suggests that BDNF in blood undergoes compensatory changes due to metabolic disorders. The subjects of the present study were participants in a medical examination (not clinical patients). Since their data for biochemical analyses were close to the reference range in many biomarkers (blood glucose level, HbA1c, TG, AST, ALT, etc.) even in the NAFLD group, they were relatively healthy subjects. Therefore, this population was considered equivalent to the prediabetes group in Liu’s study. Hashida et al. analyzed the association between the serum BDNF level and NAFLD in NAFLD patients [26]. Their study found a negative correlation between reduced activity in patients with NAFLD and the serum BDNF level. Reduction in activity leads to the progression and worsening of NAFLD symptoms. The increase in BDNF observed in the subjects of Hashida’s study may also be a compensatory change in response to the progression of NAFLD. Even in the present subjects, those with fatty liver but low serum BDNF levels may see their condition become more severe in the future. Further research with long-term follow-up is needed to test this hypothesis.

In the present study, serum BDNF, not whole blood or plasma BDNF, was measured. BDNF is present in the blood in a free state or a platelet-bound state. Since the serum BDNF level is very high compared to the plasma BDNF level, most of the BDNF in serum is released from platelets during the coagulation process [12]. BDNF mRNA is not expressed in platelets and megakaryocytes. Therefore, BDNF bound to platelets is thought to be BDNF released into the blood from other organs accumulated in platelets. Platelets are responsible for storing BDNF and transporting it to various areas of the body. Platelets are activated by agonists such as ADP to release BDNF [12]. The released BDNF is taken up from the TrkB receptor on the cell surface and promotes glucose and lipid metabolism [13, 23, 24]. BDNF is predicted to suppress fat accumulation in the liver by activating the AMPK signaling pathway and suppressing FAS activity [25]. Since the sample used in this study was serum, it is unclear whether the increased BDNF reflects free, or platelet bound BDNF. However, there are many reports that BDNF in serum fluctuates due to depression, diabetes, and dyslipidemia, and that serum BDNF reflects these fluctuations depending on the pathological condition, and it is therefore thought that it is meaningful to measure it. In the present study, the NAFLD group had a significant increase in platelets compared to the normal group.

BDNF is not a protein generally recognized as hepatokine, but it has been reported that BDNF is expressed in the liver. Therefore, it is quite possible that the source of BDNF in NAFLD is the liver. However, BDNF is also produced in peripheral tissues such as the heart, skeletal muscle, and vascular endothelial cells, and is transported by platelets. Based on this point, the source of BDNF in the NAFLD group cannot be clarified from the results of this study alone. Further empirical studies are needed.

This study has some limitations. One was the method of evaluating fatty liver. In this study, the severity of fatty liver was evaluated by ultrasound examination by well-trained sonographers. This method has been discussed with respect to issues of intra- and inter-observer’s errors, which results in less reproducibility. The most accurate quantitative method is MRI examination, but this study was targeted at examinees of a medical examination that is conducted free of charge, and thus MRI examination could not be performed due to the limited technical resource and cost. To reduce measurement error, fatty liver was evaluated based on a comprehensive evaluation by three sonographers.

The definition of NAFLD in the present study was based on alcohol intake and the degree of fat deposition in the liver. Liver fibrosis is a predictor of NAFLD deterioration and accompanying liver fibrosis increases the risk of NAFLD progressing to NASH. The FIB-4 index and NAFLD fibrosis score are often used as indicators of liver fibrosis. In the present study, NAFLD was defined as a case with fatty liver without excessive alcohol intake. The severity of NAFLD is evaluated by the degree of lipid deposition in the liver, and it was not consistent with the purpose of this study to evaluate the degree of fibrosis using the FIB-4 index. Therefore, these indicators were not considered when classifying the NAFLD group. The FIB-4 index was significantly lower in the NAFLD group than in the normal group (Table S1). There was no difference between the two groups in the proportion of participants whose FIB-4 index was above the low cutoff value (≥1.3) or above the high cutoff value (≥2.67). It appears that few participants in the present study had progressed to fibrosis. Subjects in the NAFLD group were significantly younger than those in the normal group. The formula for the FIB-4 index includes age, which indicates that the FIB-4 index depends on age, especially in elderly populations. Given this issue in the FIB-4 index calculation, a report recommended that the FIB-4 index should distinguish cutoff values by age [27], and the results in the present study may reflect this shortcoming of the FIB-4 index. Hashida’s study, like the present, did not show a correlation of serum BDNF levels in NAFLD patients with the FIB-4 index [26]. Regarding the NAFLD evaluation method in the present study, we have conducted research using a similar assessment of fatty liver and these studies have already been published [28, 29]. We intend to conduct future studies on the association between the degree of
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