Influence of increased physical activity without body weight loss on hepatic inflammation in patients with nonalcoholic fatty liver disease

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Abstract

Background: Physical activity (PA) that includes an accumulated exercise regimen that meets or exceeds a certain intensity reduces intrahepatic fat, leading to the improvement of nonalcoholic fatty liver disease (NAFLD) in afflicted patients. However, whether an increase in comprehensive PA, including activities of daily living, contributes to ameliorating the pathophysiology of NAFLD remains unclear. This study aimed to examine whether PA improves liver function in patients with NAFLD.

Methods: The study included 45 patients with NAFLD who underwent follow-up examinations at least 6 months—but no later than 1 year—after their baseline examinations. The patients were interviewed about their daily activities and exercise habits to determine whether they had engaged in at least 3 metabolic equivalents (METs) per day during the previous 6 months; the quantity of PA, expressed in Ekusasaizu (Ex) units, was calculated as METs multiplied by hours. Patients who had achieved at least a 1-Ex increase in PA per week compared to baseline at the time of their follow-up interview (the PA increase group) were compared to those whose PA was the same or lower at the time of follow-up (the PA non-increase group).

Results: There were no significant changes in all blood and biochemical parameters in the PA non-increase group at the time of follow-up when compared with baseline levels. In the PA increase group, aspartate aminotransferase, alanine aminotransferase, and γ-guanosine triphosphate levels were all significantly lower at follow-up than they were at baseline. Body weight did not change significantly from baseline to follow-up in both groups.

Conclusions: In the present study, hepatic inflammation improvement was accompanied by increased PA but not decreased body weight. Increasing PA may be effective for the improvement of hepatic inflammation even without body weight loss. Our results indicate the effectiveness of PA monitoring for the management of NAFLD.

Trial registration: UMIN-CTR, UMIN000038530

Keywords: Nonalcoholic fatty liver disease (NAFLD), Hepatic inflammation, Physical activity, Exercise guide, Metabolic equivalents (METs)
Background
Nonalcoholic fatty liver disease (NAFLD) is a condition in which fatty liver occurs in the absence of alcohol-induced liver failure or other liver diseases and is normally diagnosed via histology and imaging [1]. NAFLD is observed in approximately 30% of all Japanese people and has a male predilection [2]. The survival rate of patients with NAFLD is lower than that of the general population [3], and the incidence of cardiovascular events is higher in the former than in the latter [4]. Most patients with NAFLD have an underlying condition such as obesity, diabetes, dyslipidemia, or hypertension. Weight gain, high aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, low platelet counts, and high adipose tissue mass promote liver fibrosis [5]. Because physical activity (PA) improves obesity, blood glucose levels, and lipid concentrations while decreasing blood pressure [6], it is considered effective for managing NAFLD. A systematic review by Smart et al. revealed that exercise training improves cardiopulmonary function by decreasing intrahepatic fat and free fatty acid levels [7]. Purposely increasing PA to attain a certain minimum intensity may improve NAFLD by reducing intrahepatic fat. However, whether an increased comprehensive PA regimen comprising exercise and more vigorous daily activity affects the long-term pathophysiology of NAFLD remains unclear.

Obesity is the most important underlying etiology of NAFLD; in fact, visceral fat thickness is positively correlated with NAFLD severity [8]. As such, this study aimed to investigate the effect of PA on liver function in patients with NAFLD, with a focus on obesity.

Methods
The study included 154 patients aged 20–85 years who attended the outpatient clinic of the Department of Gastroenterology, Osaka Rosai Hospital; could independently perform activities of daily living; and were given no exercise restrictions by their doctors. Patients were excluded from enrollment in this study if they tested positive for hepatitis virus infection, had a history of alcohol consumption (> 20 g/day), had difficulty performing exercise (owing to, for example, joint pain, kidney dysfunction, or heart disease), or had an underlying mental disorder. Each patient was interviewed to ascertain his or her success at moderate exercise and daily activities of 3 metabolic equivalents (METs) or higher during the previous 6 months according to the Exercise Guide 2006, and the Ekusasai (Ex) unit of quantity, which is calculated as METs x hours, was obtained [13]. Regular exercise was defined as that which was performed at least twice weekly for 30 min using the transtheoretical model [14].
Knee extension force (KEF), which is the isometric muscle force of the lower limbs at 90° of knee flexion, was determined using a handheld dynamometer with a fixing belt (μTas F-01; Anima Corp., Tokyo, Japan) [15]. The maximum KEF values of the right and left knees were averaged and normalized by body weight to obtain body weight rates (%) (KEF/body weight × 100). In the 30-s chair-stand test, subjects were observed for how many times they could repeat standing up from a 40-cm-high chair and sitting back down during a 30-s period while their arms were crossed over their chests [16].

**Evaluation of habitual behaviors**

Data on eating behavior were obtained through individual interviews inquiring about diet during the preceding week using the recall method. Patients with a 20% higher or lower energy intake than that designated by the physician in charge (considered deviated calorie intake) were identified. The energy intake designated by the doctor was calculated with reference to light exertion (25–29 kcal/kg standard body weight), moderate exertion (30–34 kcal/kg standard body weight), and heavy exertion (≥35 kcal/kg standard body weight).

In terms of smoking habits, subjects who were daily or occasional smokers were considered present smokers, whereas those who never smoked or had not smoked during the previous 6 months were considered non-smokers.

**Statistical analysis**

Patients whose weekly PA was at least 1 Ex greater at follow-up than it was at baseline were classified into the “PA increase” group and were compared with those who had an unchanged or decreased PA (the PA non-increase group). Qualitative variables of these groups at baseline were compared using the chi-square test, whereas quantitative variables were compared using the independent t test or the Mann–Whitney U test based on the Shapiro–Wilk test for normally distributed data. Qualitative variables at baseline and follow-up in each group were compared using the chi-square test, whereas quantitative variables were compared using the paired t test or the Wilcoxon signed-rank test based on the Shapiro–Wilk test for normally distributed data. Parameters that differed significantly between the groups were analyzed for their interactions by 2-factor repeated measures analysis of variance.

Stepwise multiple regression analysis was used to determine the amount of PA change corresponding to the amount of body weight change, and eating behavior (calorie intake as directed, 1; deviated calorie intake, 2),

### Table 1 Baseline characteristics of patients with nonalcoholic fatty liver disease grouped by physical activity

| Parameters                      | Units   | Patients with no increased PA | Patients with increased PA | P value |
|---------------------------------|---------|-------------------------------|----------------------------|---------|
| NAFLD/NASH                      | n       | 7/13                          | 14/11                      | 0.231   |
| Type 2 diabetes                 | Presence (%) | 6 (30)                      | 4 (17)                     | 0.472   |
| Sex                             | Male/female | 10/10                        | 11/14                      | 0.769   |
| Age                             | years   | 61.8 ± 2.5                    | 56.5 ± 2.6                 | 0.281   |
| Body mass index                 | kg/m²   | 25.9 ± 1.1                    | 26.6 ± 0.7                 | 0.217   |
| Body mass index ≥ 25            | n (%)   | 9 (45)                        | 15 (60)                    | 0.377   |
| Waist circumference             | cm      | 89.0 ± 2.8                    | 89.9 ± 2.3                 | 0.392   |
| Skeletal mass index             | kg/m²   | 7.0 ± 0.2                     | 7.1 ± 0.2                  | 0.915   |
| Physical activity and physical function |         |                               |                            |         |
| PA for daily activities         | Ex/week | 4.6 ± 0.5                     | 3.6 ± 0.3                  | 0.189   |
| PA for exercise                 | Ex/week | 4.4 ± 1.1                     | 3.3 ± 0.9                  | 0.505   |
| Total amount of PA             | Ex/week | 9.1 ± 1.2                     | 7.0 ± 1.0                  | 0.190   |
| Regular exercise habits         | Presence (%) | 11 (55)                    | 12 (48)                    | 0.767   |
| Knee extension force            | kgf     | 32.7 ± 2.2                    | 36.0 ± 3.2                 | 0.429   |
| %Knee extension force           | %       | 49.2 ± 3.2                    | 50.3 ± 2.8                 | 0.810   |
| CS30 test                       | n       | 21.8 ± 1.1                    | 23.5 ± 1.1                 | 0.307   |

Data are presented as n (%) or mean ± standard error

NAFLD nonalcoholic fatty liver disease, NASH nonalcoholic steatohepatitis, PA physical activity, CS30 30-s chair-stand test, Ex Ei{kusa}saiz{u}, metabolic equivalent × hour (unit of quantity)
diabetes mellitus (absent, 0; present, 1), and smoking habits (absent, 0; present, 1) were included as covariates. Model 1 included the eating behavior at baseline while model 2 included that at follow-up. Diabetes mellitus and smoking habits were included in both analytic models. SPSS version 24 (IBM Corp., Armonk, NY, USA) was used for statistical analysis; the significance level was set at 5%.

Results
The mean periods between baseline and follow-up were 295.3 ± 94.6 and 280.8 ± 96.1 days in the PA non-increase and PA increase groups, respectively, indicating no significant difference. The following data were shown as the mean value and standard error.

The total Ex value at follow-up in the PA non-increase group was 6.52 ± 1.0 Ex (3.57 ± 0.60 Ex for daily activities and 3.68 ± 0.95 Ex for exercise), showing a significant decrease from baseline ($P < 0.001$). In contrast, the total Ex value at follow-up in the PA increase group was 13.18 ± 1.5 Ex (4.30 ± 0.46 Ex for daily activities and 9.08 ± 1.71 Ex for exercise), showing a significant increase over the baseline value ($P < 0.001$). There were no significant intergroup differences with respect to patient characteristics (Table 1).

Regarding eating behavior, none of the patients in either group had a caloric intake less than the designated level at baseline or follow-up; all patients with deviation had exceeded the designated caloric intake. Fourteen (70%) and 19 (76%) patients had deviated eating behaviors at follow-up in the PA non-increase and PA increase groups, respectively, indicating no significant difference from baseline in

| Table 2 | Differences in clinical parameters in patients with or without increased physical activity |
|---------|------------------------------------------|
| Parameters | Units | Baseline period | Follow-up period | $P$ value |
|---------|------------------------------------------|
| **Patients without increased PA** | | | | |
| Body weight | kg | 67.7 ± 3.8 | 68.3 ± 4.1 | 0.201 |
| Aspartic aminotransferase | IU/L | 41.9 ± 3.9 | 37.6 ± 3.4 | 0.238 |
| Alanine transaminase | IU/L | 59.2 ± 8.5 | 47.0 ± 5.8 | 0.067 |
| Platelets | $10^9$/L | 210.6 ± 16.8 | 203.1 ± 16.8 | 0.629 |
| FIB-4 index | | 2.10 ± 0.28 | 2.24 ± 0.36 | 0.459 |
| FIB-4 index $\geq$ 2.67 | n (%) | 7 (35) | 5 (25) | 0.731 |
| $\gamma$-Glutamyltransferase | IU/L | 77.4 ± 15.8 | 58.3 ± 9.0 | 0.054 |
| Lactate dehydrogenase | IU/L | 209.6 ± 11.7 | 202.4 ± 8.2 | 0.279 |
| Alkaline phosphatase | IU/L | 269.1 ± 20.6 | 269.0 ± 24.7 | 0.944 |
| Total bilirubin | mg/dL | 0.66 ± 0.16 | 0.73 ± 0.06 | 0.360 |
| Total cholesterol | mg/dL | 190.0 ± 7.6 | 191.8 ± 8.3 | 0.716 |
| Triglycerides | mg/dL | 146.7 ± 18.1 | 179.3 ± 25.6 | 0.136 |
| Albumin/globulin ratio | | 1.48 ± 0.04 | 1.46 ± 0.04 | 0.526 |
| **Patients with increased PA** | | | | |
| Body weight | kg | 69.5 ± 3.3 | 67.8 ± 3.3 | 0.104 |
| Aspartic aminotransferase | IU/L | 61.4 ± 7.8 | 37.5 ± 3.0 | 0.004 |
| Alanine transaminase | IU/L | 95.3 ± 10.8* | 49.5 ± 5.9 | < 0.001 |
| Platelets | $10^9$/L | 227.8 ± 12.8 | 231.6 ± 12.8 | 0.584 |
| FIB-4 index | | 1.77 ± 0.24 | 1.56 ± 0.20 | 0.187 |
| FIB-4 index $\geq$ 2.67 | n (%) | 5 (20) | 4 (16) | 1.000 |
| $\gamma$-Glutamyltransferase | IU/L | 89.1 ± 19.3 | 60.0 ± 11.5 | 0.015 |
| Lactate dehydrogenase | IU/L | 201.0 ± 7.5 | 194.4 ± 7.6 | 0.188 |
| Alkaline phosphatase | IU/L | 301.1 ± 33.6 | 284.9 ± 35.3 | 0.651 |
| Total bilirubin | mg/dL | 1.17 ± 0.32 | 0.93 ± 0.11 | 0.373 |
| Total cholesterol | mg/dL | 207.3 ± 9.1 | 205.9 ± 8.9 | 0.594 |
| Triglycerides | mg/dL | 186.7 ± 25.9 | 166.4 ± 31.8 | 0.292 |
| Albumin/globulin ratio | | 1.35 ± 0.05 | 1.39 ± 0.06 | 0.268 |

Data are presented as n (%) or mean ± standard error

FIB-4 fibrosis-4, PA physical activity

*P < 0.05, comparison between patients without increased PA and patients with increased PA during the baseline period
either group. Furthermore, there was no intergroup difference at follow-up; there was no significant change in smoking habits between baseline and follow-up.

There were no significant changes in any blood or biochemical parameters measured at the time of follow-up when compared to baseline measurements in the PA non-increase group (Table 2). Conversely, there was a significant decrease in AST, ALT, and γ-guanosine triphosphate (γ-GTP) levels at follow-up in the PA increase group when compared to baseline. These results indicated a significant decrease in AST, ALT, and γ-GTP levels in both groups at follow-up as well as a tendency for AST, ALT, and γ-GTP to interact, although not significantly, in both groups \( (F = 2.287, P = 0.103; F = 3.909, P = 0.055; F = 0.117, P = 0.734, \text{ respectively}) \) (Fig. 1). In stepwise multiple regression analysis, an increased PA was identified as a significant independent explanatory variable concerning the change in body weight in both analytic models (Table 3).

**Discussion**

In this study, patients with NAFLD were followed up for at least 6 months, but less than 1 year, and the specific parameters of individuals who engaged in increased PA were compared with those who did not undertake increased PA to investigate the effect of increased PA on liver function.

In a study of obese individuals, exercise therapy alone for over 12 weeks, but without dietary changes, reduced hepatic lipid levels despite no decrease in body weight [17]. Aerobic and resistive exercises improve blood glucose control, thereby improving insulin resistance and lipid metabolism. Therefore, such exercises are an established basic treatment for type 2 diabetes mellitus [18], although it may be difficult to maintain these exercise habits. In our previous study of 1442 patients with type 2 diabetes aged 30–87 years, only 26.9% exercised regularly [19]. It is also apparent that the level of daily activities is a major determinant of the differences in body weights between obese and non-obese individuals [20]; hence, exercise or daily activities may effectively manage NAFLD.

There was a significant relation between the change in body weight and PA by the multivariate analysis in this study; however, the body weight did not significantly decrease by the univariate analysis in each group. Our study did not use a uniform exercise program, and PA intensity and duration varied among patients in the PA increase group. Increasing PA is important but not equivalent to performing a regular exercise for the improvement of hepatic inflammation without weight loss.
The "Specific Health Checkups" of Japan focus on metabolic syndrome and aim to prevent lifestyle-related diseases in 40–74-year-old individuals while guiding persons at high risk of developing such diseases [21]. The Specific Health Guidance is implemented with the aim of maintaining increased PA rather than confining exercise to a specific time frame during the day per the Exercise Guide 2006 [22]. In our study, an increase in non-standardized PA did not lead to body weight loss but improved hepatic inflammation, indicating the effectiveness of the Exercise Guide 2006 in the management of NAFLD. Interestingly, univariate analysis revealed a significant association between the decrease in laboratory findings reflecting hepatic inflammation, and the increase in PA; however, multivariate analyses revealed no significant interactions between each group. Attention should be paid for a better understanding of these results based on statistical analysis.

This study had several limitations. First, PA was evaluated in terms of the Ex value, and patients who had increased their PA by at least 1 Ex at follow-up relative to that at baseline were classified into the PA increase group. Although the mean increase was 6 Ex, the degree of effective increase in Ex remains unclear. In addition, patients were followed up for at least 6 months, and as a result, the end points in both groups were not unified. These differences may have resulted in endpoint variability. Second, the AST, ALT, and γ-GTP levels significantly decreased at follow-up in the PA increase group when compared to those at baseline. However, baseline ALT values were significantly higher in the PA increase group than in the PA non-increase group, and this may have influenced our results. Third, PA was evaluated according to the Exercise Guide 2016; therefore, it is unclear whether the actual exercises or the daily activities were responsible for greater body weight loss and improved hepatic inflammation. Furthermore, the evaluation and teaching methods based on the Exercise Guide 2006 were subjective. Therefore, it may be necessary to objectively quantify PA with a smart device. Fourth, the methodology of our study did not allow us to determine whether diet exerted an independent or synergistic effect on improving hepatic inflammation and body weight loss. Moreover, eating behaviors were evaluated based on the energy intake data from the previous week at both baseline and follow-up, as designated by the physician in charge. Therefore, the effects of eating behaviors during the period between baseline and follow-up are uncertain. Fifth, the study design prevented the evaluation of any synergistic effects of PA and diet. Further investigations are necessary to address these remaining issues.

### Table 3

Stepwise multiple regression analysis using body weight change as the objective variable

| Explanatory variable                  | β   | t value | P value | VIF |
|--------------------------------------|-----|---------|---------|-----|
| Change in total amount of PA         | −0.390 | −2.622 | 0.012   | 1.046 |
| Baseline eating behavior             | 0.009 | 0.057 | 0.954   | 1.076 |
| Presence of diabetes                 | 0.111 | 0.750 | 0.458   | 1.037 |
| Smoking habits                       | 0.116 | 0.759 | 0.452   | 1.101 |
| Change in total amount of PA         | −0.398 | −2.717 | 0.010   | 1.048 |
| Follow-up eating behavior            | 0.157 | 1.078 | 0.288   | 1.030 |
| Presence of diabetes                 | 0.095 | 0.647 | 0.521   | 1.042 |
| Smoking habits                       | 0.098 | 0.669 | 0.507   | 1.044 |

VIF: Variance inflation factor; PA: Physical activity

### Conclusions

We noted significant improvements in ALT, AST, and γ-GTP levels in the PA increase group, which comprised subjects with increased PA by a mean of 6 Ex at follow-up compared to baseline. In contrast, while there were non-significant improvements in the blood and biochemical parameter measurements of the PA non-increase group, these differences were not as high as those observed in the PA increase group. Our data indicated that increased PA improves hepatic inflammation but does not decrease body weight in patients with NAFLD. Increasing PA may be effective for the improvement of hepatic inflammation without decreasing body weight. PA monitoring is important for the management of NAFLD.

### Abbreviations

- ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Ex: Ekusasai (unit); KEF: Knee extension force; MET: Metabolic equivalent; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; PA: Physical activity; γ-GTP: γ-Guanosine triphosphate

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### Authors’ contributions

FA, TN, AH, and MK contributed to the study conception and design. FA and TN performed the material preparation, data collection, and analysis. TN wrote the first draft of the manuscript. All authors commented on the subsequent versions. All authors read and approved the final manuscript.

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### Availability of data and materials

The datasets supporting the conclusions of this article are available from the corresponding author upon reasonable request.

### Ethics approval and consent to participate

The Research Ethics Committee of Osaka Rosai Hospital approved the study (approval number: 20130215). The patients provided written informed consent for inclusion in the study.
Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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