Exacerbation of liver dysfunction in non-alcoholic steatohepatitis patients during the coronavirus disease 2019 (COVID-19) pandemic

Akira Asai,* Hidetaka Yasuoka, Masahiro Matsui, Norio Okamoto, Shinya Fukunishi, and Kazuhide Higuchi

2nd Department of Internal Medicine, Osaka Medical College, 2-7 Daigakumachi, Takatsuki, Osaka 569-8686, Japan

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Many people were forced to stay at home, including non-alcoholic steatohepatitis (NASH) patients, however it is unclear how this home-life has affected the prognosis of NASH. In this study, we examined the influences of living at home during the coronavirus disease 2019 (COVID-19) pandemic NASH patients. In this study, we compared the clinical parameters of NASH patients without COVID-19 infection 3 months before with those 3 months after the declaration of a state of emergency. In the results, the changes of aspartate transaminase and alanine aminotransferase in the 3 months before (aspartate transaminase, –3.6 ± 13.8 U/L; alanine aminotransferase, –6.8 ± 19.5 U/L) was significantly exacerbated in the 3 months after (aspartate transaminase, 2.3 ± 7.5 U/L; alanine aminotransferase, 1.7 ± 10.4 U/L). Furthermore, the changes of the fibrosis-4 index in the 3 months before (–0.27 ± 0.84) was also significantly exacerbated in the 3 months after (0.38 ± 0.96). In conclusion, liver dysfunctions in NASH patients were exacerbated due to the emergency declaration and outing restriction which accompanied COVID-19.

Key Words: NASH, COVID-19, liver dysfunction

Non-alcoholic steatohepatitis (NASH) is defined as a condition characterized by deposition of fat in at least 5% of hepatocytes in the absence of secondary causes of lipid accumulation or those attributable to consumption of alcohol. NASH is a cause of cirrhosis and hepatocellular carcinoma.(1) Over the past decade, the incidence of NASH, a lifestyle-related disease, has grown.(2,3) Treatments with various drugs have been tried, but no evidence-based treatment has emerged. Lifestyle modifications such as exercise, diet and weight loss have been advocated as the most effective treatment.(4)

From the end of 2019, coronavirus disease 2019 (COVID-19) has been an emerging infectious disease, initially mainly in China, but it has since spread all over the world. The number of COVID-19 patients dying from the severe acute respiratory syndrome caused by this virus is increasing worldwide.(5) Since this virus is considered to cause infection through contact and airborne transmission declaration of a state of emergency and outing restrictions have been applied around the world, mainly in countries where the infection is increasing.(6) Invariably, an declaration of a state of emergency was issued in Japan from April 7, 2020 to May 26, 2020 to prevent the spread of COVID-19 infections. Many people were forced to stay at home, including NASH patients, however it is unclear how this home-life has affected the prognosis of NASH. In this study, we examined the influences of living at home during the COVID-19 epidemic on NASH patients.

Methods

NASH patients. This study was approved by the Institutional Review Board of the Osaka Medical College (IRB approved number: 2020-066) and was conducted in accordance with the relevant guidelines and regulations of the Osaka Medical College. Informed consent was obtained in the form of opt-out on the web-site. Those who rejected were excluded. In this study, we enrolled 259 patients who were diagnosed with NASH and had a follow-up visit at the Osaka Medical College. First, the following 199 patients were excluded: 31 patients with hepatocellular carcinoma or other cancers, 4 patients with decompensated cirrhosis, 51 patients with other liver disease (hepatitis B virus, hepatitis C virus, primary biliary cholangitis, autoimmune hepatitis, and infection), 6 patients who were diagnosed with NASH within the last 6 months, and 107 patients without blood tests. Second, 30 patients who canceled their follow-up visit themselves were excluded. Ultimately, 30 patients were eligible for this study. These patients did not have symptoms of COVID-19; which include shortness of breath, achés, nasal congestion, sore throat, cough, and fever.

Clinical parameters. In these patients, the clinical parameters from blood samples taken both 6 and 3 months before, during and 3 months after the duration of declaration of a state of emergency, were compared. The fibrosis-4 (FIB-4) index was calculated by this equation.(7)

\[
\text{FIB-4 index} = \frac{(\text{Age (years)} \times \text{aspartate transaminase (AST) (U/L)})}{\text{platelet (10^3)} \times \sqrt{\text{alanine aminotransferase (ALT) (U/L)}}}
\]

Statistical analysis. Statistical analyses were performed using JMP Pro software ver. 14 (Tokyo, Japan). Differences of quantitative values in two groups were analyzed using a Mann–Whitney U test and in three groups were Kruskal-Wallis test. The Fisher’s exact test was used to analyze the nominal scales. A \(p\) value <0.05 was considered statistically significant.

Results

Four patients were diagnosed with NASH-related liver cirrhosis, with a Child-Pugh score of 5. Ten patients were treated with a combination of calorie reduction, exercise, and healthy eating. The other 20 patients received drug treatment in addition to those lifestyle modifications (Table 1A). In these patients, 3 months before the declaration of a state of emergency, the

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*To whom correspondence should be addressed.
E-mail: in2108@osaka-med.ac.jp
Table 1. Patient characteristics

(A) Baseline characteristics of patients

| Characteristic                      | n = 30                  |
|-------------------------------------|-------------------------|
| **Age (year, range)**              | 62.7 (42–84)            |
| **Gender (male/female)**           | 12/18                   |
| **CH/LC**                          | 26/4                    |
| **DM (+/–)**                       | 14/16                   |
| **HT (+/–)**                       | 6/24                    |
| **HL (+/–)**                       | 13/17                   |
| **Right hand grip (kg, mean ± SD)**| 24.8 ± 9.4              |
| **Left hand grip (kg, mean ± SD)** | 22.9 ± 8.8              |
| **BH (m, mean ± SD)**              | 1.60 ± 0.08             |
| **BW (kg, mean ± SD)**             | 65.7 ± 11.8             |
| **BMI (kg/m², mean ± SD)**         | 25.5 ± 4.0              |
| **Drug treatment (+/–)**           | 20/10                   |

BH, body height; BMI, body mass index; BW, body weight; CH, chronic hepatitis; DM, diabetes mellitus; HL, hyperlipemia; HT, hypertension; LC, liver cirrhosis.

(B) Patient laboratory findings

| Parameter                        | 0 Month (n = 30) | 3 Month (n = 30) | 6 Month (n = 30) | p values |
|----------------------------------|-----------------|-----------------|-----------------|----------|
| Alb (g/dl, mean ± SD)            | 4.21 ± 0.32     | 4.18 ± 0.34     | 4.16 ± 0.41     | 0.86     |
| T-Bil (mg/dl, mean ± SD)         | 0.70 ± 0.32     | 0.73 ± 0.36     | 0.70 ± 0.44     | 0.84     |
| AST (U/L, mean ± SD)             | 37.3 ± 16.7     | 33.7 ± 14.8     | 36.0 ± 15.4     | 0.66     |
| ALT (U/L, mean ± SD)             | 45.4 ± 29.9     | 38.5 ± 24.7     | 40.3 ± 26.4     | 0.6      |
| T-cho (mg/dl, mean ± SD)         | 193.6 ± 49.2    | 193.8 ± 33.7    | 198.3 ± 40.9    | 0.9      |
| TG (mg/dl, mean ± SD)            | 119.9 ± 50.5    | 122.7 ± 59.3    | 142.2 ± 63.0    | 0.32     |
| Plt (×10⁴/μl, mean ± SD)         | 20.8 ± 8.5      | 20.7 ± 8.1      | 20.2 ± 8.2      | 0.95     |
| Prothrombin time (% ± SD)        | 95.3 ± 17.5     | 97.7 ± 13.0     | 93.2 ± 20.5     | 0.65     |
| FIB4-index (mean ± SD)            | 2.47 ± 2.31     | 2.20 ± 1.65     | 2.59 ± 2.36     | 0.77     |

Alb, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; Plt, platelet; T-Bil, total bilirubin; T-cho, total cholesterol; TG, triglyceride.

Fig. 1. Changes in the clinical parameters of NASH in patients before and after the declaration of a state of emergency. The clinical parameters (AST, ALT, T-cho, triglyceride, and FIB4-index) from blood samples taken both 6 and 3 months before, during and 3 months after the duration of declaration of a state of emergency, were compared.
treatment had improved the serum AST and ALT. The fibrosis-4 (FIB-4) index score, a noninvasive fibrotic marker of the liver, also decreased. However, no significant difference was observed in each parameter. Albumin, total bilirubin, total cholesterol (T-cho), platelets, and prothrombin time did not change. In contrast; AST, ALT, T-cho, triglyceride, and the FIB4-index score increased in these patients in the 3 months after the declaration of a state of emergency (Table 1B).

When we compared the changes between the 3 months before and after the declaration of a state of emergency, the changes of AST, ALT, and FIB4-index in the 3 months before (AST, $-3.6 \pm 13.8$ U/L; ALT, $-6.8 \pm 19.5$ U/L; FIB-4 index, $-0.27 \pm 0.84$) was significantly exacerbated in the 3 months after the declaration of a state of emergency (AST, $2.3 \pm 7.5$ U/L; ALT, $1.7 \pm 10.4$ U/L; FIB-4 index, $0.38 \pm 0.96$) (Fig. 1). These results suggest that liver dysfunctions in NASH patients were exacerbated due to the emergency declaration and outing restriction which accompanied COVID-19.

Discussion

Although there are many diseases that are exacerbated by COVID-19 infection, this study revealed that liver dysfunctions in NASH patients, in the absence of COVID-19 infection, was exacerbated by the new lifestyle that resulted from the COVID-19 pandemic. Similar exacerbations may be detected in other lifestyle-related diseases such as diabetes, hypertension, and abnormal lipid metabolism. Also, it was reported that the malnutrition and selective IgA deficiency were detected in patients with COVID-19 (8,9).

In this study; the AST, ALT, and FIB-4 index were clearly raised suggesting that liver fibrosis may have progressed. In order to clarify this, it is important to evaluate hepatic fibrosis by pathological analysis with a liver biopsy or by measuring non-invasive liver stiffness with abdominal ultrasonography. However, it is not as easy to carry out these procedures as we did before, since visiting the hospital carries increased risk of COVID-19 infection. In future, these evaluations will need to be performed after ensuring safety against COVID-19.

One of the limitations of this study is that its sample size was comparatively small. Half of the patients cancelled their follow-up visit. The influence of staying at home on the liver function of the patients who canceled is unknown and assessing liver function in these patients poses a problem in the future.

Acknowledgments

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Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| Alb          | albumin     |
| ALT          | alanine aminotransferase |
| AST          | aspartate transaminase |
| BH           | body height |
| BMI          | body mass index |
| BW           | body weight |
| CH           | chronic hepatitis |
| COVID-19     | coronavirus disease 2019 |
| DM           | diabetes mellitus |
| FIB-4        | the fibrosis-4 |
| HL           | hyperlipemia |
| HT           | hypertension |
| LC           | liver cirrhosis |
| NASH         | non-alcoholic steatohepatitis |
| Plt          | platelet |
| T-Bil        | total bilirubin |
| T-cho        | total cholesterol |
| TG           | triglyceride |

Conflict of Interests

No potential conflicts of interest were disclosed.

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