Original Article

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

(Received 17 August, 2020; Accepted 17 September, 2020; Published online 3 December, 2020)

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, aches, 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]

$$\text{FIB-4 index} = \frac{[\text{Age (years)} \times \text{aspartate transaminase (AST) (U/L)}]}{[\text{platelet } (10^9) \times \sqrt{\text{alanine aminotransferase (ALT) (U/L)}}]}$$

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

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

doi: 10.3164/jcbn.20-136

Table 1. Patient characteristics

(A) Baseline characteristics of patients

	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/m^2, 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

	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	0.76 ± 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 (×10^4/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.

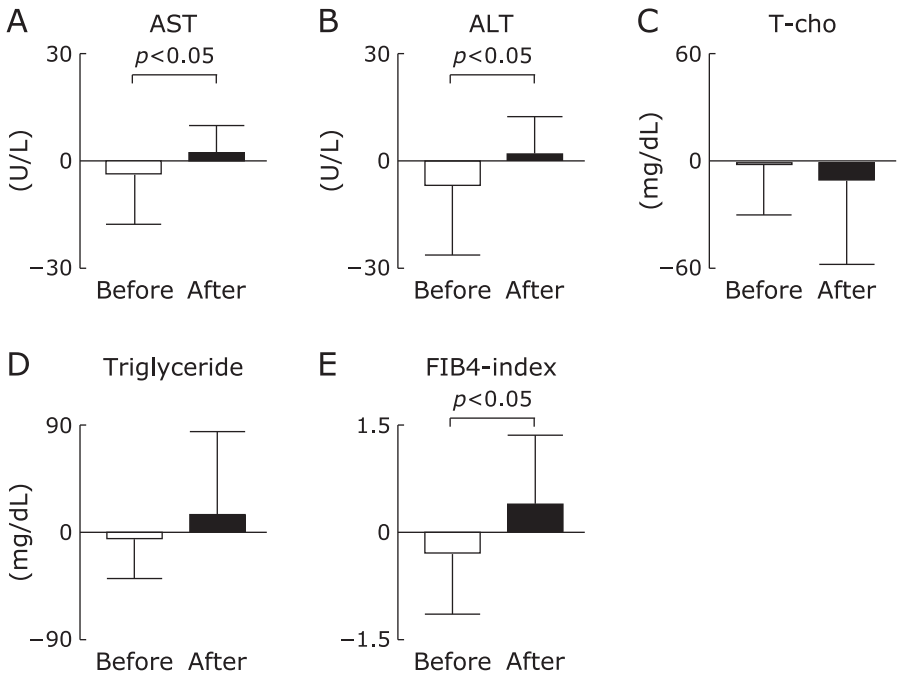

Fig. 1. Changes in the clinical parameters of NASH in patients before and after the declaration of a state of emergency. The clinical parameters (AST, ALT, T-cho, triglyceride, and FIB4-index) from blood samples taken both 6 and 3 months before, during and 3 months after the duration of declaration of a state of emergency, were compared.

doi: 10.3164/jcbn.20-136

treatment had improved the serum AST and ALT. The fibrosis-4 (FIB-4) index score, a noninvasive fibrotic marker of the liver,[6] 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 ± 13.8 U/L; ALT, –6.8 ± 19.5 U/L; FIB-4 index, –0.27 ± 0.84) was significantly exacerbated in the 3 months after the declaration of a state of emergency (AST, 2.3 ± 7.5 U/L; ALT, 1.7 ± 10.4 U/L; FIB-4 index, 0.38 ± 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

This study was supported by OMC Internal Research Grant.

Abbreviations

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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