Original Article

Questionnaire survey on lifestyle of patients with nonalcoholic steatohepatitis

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Lack of exercise and excessive food intake are known to be the important causes of nonalcoholic steatohepatitis (NASH). To elucidate the relationship between lifestyle and NASH, we surveyed exercise and dietary habits, comparing them among 171 biopsy-proven NASH patients, 29 nonalcoholic fatty liver (NAFL) patients and 49 normal subjects. Dietary habits including the duration of dinner time, amount of rice at dinner, and weekly frequencies of meat, fries, Chinese noodles, sweets, and instant food consumption were significantly different in male NASH patients compared to normal male subjects. In women, differences were seen in the amount of rice at dinner, frequency of eating out, and proclivity for sweets. In male NASH patients, the frequency of physical exercise was significantly lower. The lifestyle tendencies of NASH were almost similar to those of NAFL. In the comparison between obese NASH and non-obese NASH, no clear lifestyle differences were found. In conclusion, the most striking result of this survey was that the lifestyle of males contributed significantly to the development of NASH. These results point to treatment of NASH in males. In female NASH patients, lifestyle differences were minimal, and the effects of other factors such as genetic background will need to be investigated.

***Key Words*: NASH, lifestyle, exercise, gender, dietary habit**

In recent years, with increases in overeating, Western food intake, and the use of automobiles instead of walking in Japan, the rates of obesity and lifestyle-related diseases such as type 2 diabetes mellitus have been on the rise. Non-alcoholic fatty liver disease (NAFLD) has recently been recognized as a leading cause of abnormal liver function.[1] Its spectrum ranges from fatty liver alone, usually a benign and non-progressive condition, so-called nonalcoholic fatty liver (NAFL), to non-alcoholic steatohepatitis (NASH), which may progress to liver cirrhosis and hepatocellular carcinoma.[2–4] Patients with NASH are usually complicated by insulin resistance syndrome.[5] Diet and lack of exercise are strongly related to the development of insulin resistance.[6,7] It has been reported that high-fat Western food and glycemic load are positively associated with fat deposits and insulin resistance.[8] On the other hand, even moderate exercise is effective for the improvement of insulin resistance.[9] However, there are few reports about the association of detailed lifestyle variables, such as food preferences and exercise habits, with the development or progression of NASH/ NAFLD.

In addition, we were interested in the difference between obese-NASH and non-obese NASH. In case of non-obese NASH, it is not clear whether genomic background or lifestyle has more impact on the occurrence of NASH.

The aim of this study was to clarify the kind of lifestyle variables involved in the development and occurrence of obese and non-obese NASH.

Materials and Methods

One hundred seventy-one Japanese patients histologically diagnosed with NASH at Tokyo Women's Medical University between 1995 and 2010 were evaluated, along with 49 healthy subjects serving as controls. The diagnosis of NASH was established based on the following criteria: (1) Histologically, macrovesicular steatosis affecting at least 5% of hepatocytes with lobular inflammation, ballooning degeneration and/or perivenular or/and pericellular fibrosis.[10,11] (2) Intake of less than 140 g of ethanol per week, as confirmed by physicians and family members. (3) Appropriate exclusion of other liver diseases such as alcoholic liver disease, viral hepatitis, autoimmune hepatitis, drug-induced liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, and metabolic liver diseases. In all NASH patients, liver biopsy was performed. Fibrosis was scored using a 5-grade scale: F0, normal connective tissue; F1, foci of perivenular or pericellular fibrosis in zone 3; F2, perivenular or pericellular fibrosis confined to zones 2 and 3, with or without portal/periportal fibrosis; F3, bridging or septal fibrosis; F4, cirrhosis.[10,11] Steatosis was graded on a scale of 1 to 3: 1, mild (affecting 10–33% of hepatocytes); 2, moderate (33–66% of hepatocytes); 3, severe (>66% of hepatocytes). Ballooning degeneration was graded on a scale of 1 to 2: 1 mild or moderate; 2, severe. In addition, the NAFLD activity score (NAS) was assessed.[12] We added 29 NAFL patients. Six patients were diagnosed by liver biopsy and 23 patients by NAFIC score.[13] Liver biopsy showed steatosis without ballooning degeneration, or NAFIC scores were 0 or 1. There was no HCC case in NASH and NAFL. The 49 Japanese control subjects were matched for age and gender with the NASH patients. All control subjects previously having undergone ultrasonographic examination confirming the absence of steatosis were confirmed by blood test to have normal liver function and to be free of viral hepatitis infection. The NASH patients and control subjects were asked about their dietary habits and exercise routines.

The survey included the following questions: Question (Q.) 1) Do you have breakfast every day? Q.2) How long do you take to have dinner? Q.3) How many bowls of rice do you eat at dinner? Q.4) How many times per week do you eat meat dishes? Q.5) How many times per week do you eat fries? Q.6) How many times per week do you eat Chinese noodles? Q.7) How many times per week do you eat out? Q.8) How many times per week do you eat instant food? Q.9) How many times per week do you eat fast food? Q.10) How many cans of coffee or juice do you drink per week? Q.11) How many times per week do you eat sweets? Q.12) How many times per week do you eat cake? Q.13) Do you do exercise at least once a week? Q.14) Do you prefer to use the elevator or stairs? Q.15) Do you travel to work by car or train? These questions were

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answered on paper forms, and the answers of NASH patients, NAFL patients and normal subjects were compared.

Obesity was defined as a BMI>25 kg/m^2 according to the Japanese Obesity Association criteria. Diagnosis of type II diabetes mellitus (DM) was based on the WHO criteria. The diabetes criteria of WHO is almost the same as Japanese criteria. Briefly, fasting plasma glucose ≥126 mg/dl or 2-h plasma glucose of ≥200 mg/dl. Dyslipidemia was diagnosed if the patient was currently on treatment with lipid-lowering medications or had elevated serum levels of total cholesterol (>220 mg/dl) and/or triglycerides (>150 mg/dl) on at least 3 occasions. Hypertension was diagnosed if the patient was receiving antihypertensive therapy or had a blood pressure >140/90 mmHg on at least 3 occasions.

Brinkman index, the number of cigarettes smoked per day multiplied by the years of smoking, was used for smoking assessment.

In addition, the answers were compared between mild fibrosis NASH patients (F0–2) and severe fibrosis (F3–4) NASH patients, between NAS 5 points or over and NAS 4 points or under,[12] between mild steatosis (S1–2) and severe steatosis (S3), between mild-moderate ballooning degeneration and severe ballooning degeneration, and between obese NASH (BMI >25 kg/m^2) and non-obese NASH. We also compared non-obese NASH or non-obese NAFL with non-obese control subjects.

Statistical analysis. The results were expressed as mean percentage or times. The Mann-Whitney U test or χ^2 test was used to find differences between NASH patients or NAFL patients and control subjects. A p value of <0.05 was considered to be statistically significant in all analyses.

Results

Table 1 shows the profile of NASH, NAFL patients and control subjects. There were no age differences among the male NASH patients, male NAFL patients and male control, nor among the female NASH patients, female NAFL patients and female controls. In both male and female NASH patients, the prevalence of obesity, DM, and body weight gain ≥10 kg compared to their 20-year-old body weights were significantly higher than in the respective control subjects. There is no significant differences between male NASH and male NAFL, and between female NASH and female NAFL.

Comparison of lifestyle among NASH, NAFL and control subjects. The results of the questionnaire survey are shown below (Table 2). Q.1) Skipping breakfast: no difference between NASH and control subjects in both females and males. Q.2) Time required for dinner: a higher percent of <30-min dinners in male NASH patients than in male controls (male NASH, 71%, male control, 43%); no difference in females. Q.3) Number of bowls of rice at dinner: percent who eat >one bowl significantly higher in NASH patients in both females and males than controls (male NASH, 56%, male controls, 29%, female NASH, 18%, female controls, 0%). Q.4) Meat dishes: percent who eat meat 3 times or

Table 1. Patient profile

	Male			Female		
	NASH	NAFL	Control	NASH	NAFL	Control
Number	93	16	21	78	13	28
Age (average)	45	49	46	58	61	54
Obesity (BMI >25) (%)	77.4**	68.8▲▲	9.5	59**	69.2▲▲	3.6
DM (%)	25.8*	12.5	4.8	42.3**	30.8▲	3.6
HT (%)	32.3	56.3▲	14.3	42.3**	46.2▲▲	3.6
Dyslipidemia (%)	34.4	50▲	14.3	44.9**	69.2▲	10.7
Ethanol (g/week) (average)	29.2	62.1	62.7	7.6	9.4	54.4
Brinkman index (average)	198	109.1	63	57	93.8	4
+10 kg weight gain (%) (compare to their twenties)	50.5*	56.3▲	23.8	62.8**	53.8▲▲	7.1
Serum ALT (IU/L)	108 ± 84	73 ± 56	23 ± 8	86 ± 81	32 ± 19	21 ± 7

NASH vs Control *p<0.05, **p<0.01; NAFL vs Control ▲p<0.05, ▲▲p<0.01. There is no difference between NASH and NAFL.

Table 2. The results of the questionnaire survey among NASH, NAFL , and control subjects

	Male			Female		
	NASH	NAFL	Control	NASH	NAFL	Control
Q.1) Having breakfast everyday	59/93 (63%)	10/16 (63%)	13/21 (62%)	54/78 (69%)	9/13 (69%)	22/28 (79%)
Q.2) Time required for dinner (<30 min)	66/93 (71%)*	10/16 (63%)	9/21 (43%)	42/78 (54%)	8/13 (62%)	11/28 (39%)
Q.3) Rice at dinner (>1 bowl of rice)	52/93 (56%)*	7/16 (44%)	6/21 (29%)	14/78 (18%)*	2/13 (15%)△	0/28 (0%)
Q.4) Meat dishes (≥3 times per week)	67/93 (72%)**	8/16 (50%)	8/21 (38%)	39/78 (50%)	8/13 (62%)	20/28 (71%)
Q.5) Fries (≥3 times per week)	44/93 (47%)**	3/16 (19%)	1/21 (5%)	19/78 (24%)	2/13 (15%)	4/28 (14%)
Q.6) Chinese noodles (≥3 times per week)	48/93 (52%)**	6/16 (38%)	4/21 (19%)	31/78 (40%)	4/13 (31%)	12/28 (43%)
Q.7) Eating out (≥3 times per week)	50/93 (54%)	9/16 (56%)	8/21 (38%)	30/78 (39%)*	2/13 (15%)	4/28 (14%)
Q.8) Instant food (≥2 times per week)	41/93 (44%)**	6/16 (38%)△	1/21 (5%)	19/78 (24%)	1/13 (8%)	5/28 (18%)
Q.9) Fast food (≥once per week)	41/93 (44%)	5/16 (31%)	5/21 (24%)	31/78 (40%)	3/13 (23%)	6/28 (21%)
Q.10) Canned coffee or juice (≥3 bottles per week)	17/93 (18%)	1/16 (6%)	3/21 (14%)	5/78 (6%)	1/13 (8%)	0/28 (0%)
Q.11) Sweets (≥0.5 times per week)	73/93 (79%)**	10/16 (63%)	7/21 (33%)	59/78 (76%)*	6/13 (46%)	12/28 (43%)
Q.12) Cakes (≥once per week)	27/93 (29%)	3/16 (19%)	6/21 (29%)	27/78 (35%)	2/13 (15%)	8/28 (29%)
Q.13) No regular exercise	73/93 (79%)*	12/16 (75%)	12/21 (57%)	59/78 (76%)	10/13 (77%)	16/28 (57%)
Q.14) Elevator/escalator (prefer to use)	66/93 (71%)*	10/16 (63%)	10/21 (48%)	55/78 (71%)	8/13 (62%)	18/28 (64%)
Q.15) Commuting method (percentage of cars)	10/93 (11%)**	4/16 (25%)	10/21 (48%)	2/78 (3%)**	1/13 (8%)	6/28 (21%)

Q, question; NASH vs Control *p<0.05, **p<0.01; NAFL vs Control △p<0.05, △△p<0.01. There is no difference between NASH and NAFL.

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more per week significantly higher in male NASH patients than in male controls (male NASH, 72%; male control, 38%); no difference in females. Q.5) Fries: percent who eat fries 3 times or more per week significantly higher in male NASH patients than in male controls (male NASH, 47%; male control, 5%); no difference in females. Q.6) Chinese noodles: percent who eat Chinese noodles 3 times or more per week significantly higher in male NASH patients than in male controls (male NASH, 52%; male control, 19%); no difference in females. Q.7) Eating out: percent who eat out 3 times or more per week higher in female NASH patients than in female controls (female NASH, 39%; female control, 14%); no difference in males. Q.8) Instant foods: percent of eating instant foods 2 times or more per week significantly higher in male NASH patients than in male controls (male NASH, 44%; male control, 5%); no difference in females. Q.9) Fast food: percent who eat fast food once a week, no difference. Q.10) Coffee or juice cans: no difference between NASH and control subjects. Q.11) Sweets: frequency of eating sweets, higher in both male and female NASH patients than in respective controls (male NASH, 79%; male control, 33%; female NASH, 76%; female controls, 43%). Q.12) Cakes: frequency of eating cake once or more per week, no difference between NASH and control subjects. Q.13) Regular exercise: frequency of no exercise in male NASH patients significantly higher than in male controls (male NASH, 79%; male control, 57%); no difference in females. Q.14) Elevator: frequency of using elevator in male patients significantly higher than in male controls (male NASH, 71%; male control, 48%). Q.15) Commuting method: percentage of cars significantly lower in NASH patients in both females and males than in controls (male NASH, 11%: male control, 48%; female NASH, 3%; female control, 21%).

A comparison of NASH with NAFL showed no significant difference (Table 2).

Multivariate analysis was used for the comparison between male NASH and male controls, and 1) frequency of >one bowl of rice at dinner (Q.3) (p value, 0.007; Odds ratio, 25.9; 95% confidence interval 2.40–28.1), 2) frequency of eating meat 3 times or more per week (Q.4) (p value, 0.018; Odds ratio, 30.7; 95% confidence interval 1.80–523.5), and 3) frequency of using elevator (Q.14) (p value, 0.048; Odds ratio, 16.06; 95% confidence interval 1.03–250.7) were selected as independent variables.

Relationship between lifestyle and histological findings. When comparing the lifestyle factors between severe fibrosis (F3–F4) and mild fibrosis (F0–F2) of NASH, the frequency of eating cakes (Q.12) was higher in both male and female patients with severe fibrosis than in patients with mild fibrosis (Fig. 1). The other factors showed no differences between severe fibrosis and mild fibrosis.

Among NASH, the male NASH patients with 5 NAS points and over had high frequencies of rice (Q.3), Chinese noodles (Q.6) and instant food (Q.8). The female NASH patients with 5 NAS points and over had high frequencies of Chinese noodles (Q.6), and instant food (Q.8).

Regarding the relationship with steatosis grade, the male NASH patients with severe steatosis (S3) had high frequency of rice (Q.3). The female NASH patients with severe steatosis had high frequency of ≥10 kg body weight gain, and rice (Q.3). Regarding the relationship with ballooning, there were no significant differences in both male and female groups.

Lifestyle of non-obese NASH. Table 3 compares the questionnaire answers of obese NASH and non-obese NASH patients. The average age was younger in male obese NASH than in non-obese NASH. Average Brinkman index was higher in female obese NASH. In female NASH, obese patients had a higher prevalence of body weight gain (10 kg gain since their twenties). In male obese NASH patients, the amount of rice (Q.3) was larger and intake of instant food (Q.8) was smaller. Other questions were not different between obese NASH and non-obese NASH.

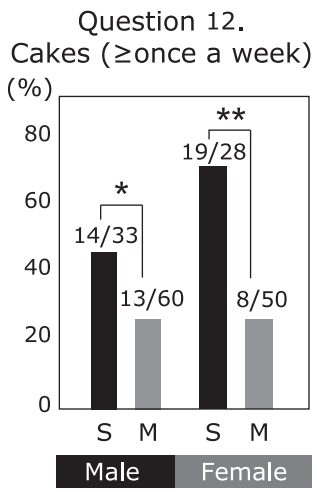

Fig. 1. The comparison of the frequency of eating cakes between severe fibrosis and mild fibrosis in NASH. The frequency of eating cakes once or more per week was significantly higher in NASH patients with severe fibrosis than in NASH patient with mild fibrosis. S; severe fibrosis, M; mild fibrosis, *p<0.05, **p<0.01.

Table 4 compares the questionnaire answers of non-obese NASH, non-obese NAFL, or non-obese control subjects. In males, non-obese NASH patients had a higher prevalence of body weight gain (≥10 kg gain since their twenties), larger intake of fries (Q.5), Chinese noodles (Q.6), and instant food (Q.8), compared to non-obese control. In females, DM, dyslipidemia, and ≥10 kg body weight gain were significantly different between non-obese NASH and non-obese control subjects. But there were no significant differences between non-obese NASH and non-obese NAFL.

Discussion

Our results suggested that dietary and exercise habits contributed to the development of male NASH. Yatsuji *et al.*[14] reported that, in Japan, about 55% of male NASH patients are under 45 years old, whereas only about 10% of female NASH patients are in this age category. Age and gender influence appetite and food preference, and other lifestyle factors. Overeating is rare in older women. Our data from single nucleotide polymorphism (SNP) analysis of the adiponectin gene revealed that the frequencies of adiponectin SNP sites were significantly different between NAFLD patients and controls in females only, not in males.[15] Several papers have reported the SNP of patatin-like phospholipase domain-containing protein 3 (PNPLA-3) gene played important role in occurrence and progression of NASH.[16–18] In a meta analysis, the influence of PNPLA-3 SNP was more powerful in female NAFLD patients.[16] These data suggest that our survey results are reasonable, pointing to the strong possibility that female NASH is influenced not so much by lifestyle but rather by genomic background. In addition, Yatsuji *et al.*[14] reported that DM was more prevalent in older female NASH patients. In our study DM was more common in female than male NASH patients. As many studies have suggested that genomic background is involved in the pathogenesis and occurrence of type 2 DM,[19,20] this data also suggest the role of genomic background in female NASH/NAFLD. In males, by contrast, our data suggested that overeating and less exercise play more important roles in NASH.

The importance of exercise was re-confirmed by our study. Streenivasa *et al.*[21] reported that daily aerobic exercise helped in normalizing ALT levels in NAFLD. Even if exercise is done at

Table 3. The comparison between obese NASH and non-obese NASH

	Male NASH		Female NASH	
	Obese	Non-obese	Obese	Non-obese
Number	73	20	46	32
Age (average)	43*	53	57	60
Ethanol (g/week) (average)	33	15	9	6
Brinkman index (average)	218	126	96*	0
DM	18/73 (25%)	6/20 (30%)	20/46 (44%)	13/32 (41%)
HT	27/73 (37%)	3/20 (15%)	19/46 (41%)	16/32 (50%)
Dyslipidemia	26/73 (36%)	5/20 (25%)	21/46 (46%)	14/32 (44%)
10 kg BW gain (compare to their 20's)	40/73 (55%)	7/20 (35%)	39/46 (85%)**	9/32 (28%)
Q.1) Having breakfast everyday	48/73 (66%)	11/20 (55%)	28/46 (61%)	26/32 (81%)
Q.2) Time required for dinner (<30 min)	54/73 (74%)	12/20 (60%)	26/46 (57%)	16/32 (50%)
Q.3) Rice at dinner (>1 bowl of rice)	45/73 (62%)*	7/20 (35%)	10/46 (22%)	4/32 (13%)
Q.4) Meat dishes (≥3 times per week)	54/73 (74%)	13/20 (65%)	25/46 (54%)	14/32 (44%)
Q.5) Fries (≥3 times per week)	35/73 (48%)	9/20 (45%)	10/46 (22%)	9/32 (28%)
Q.6) Chinese noodles (≥3 times per week)	38/73 (52%)	10/20 (50%)	20/46 (44%)	13/32 (41%)
Q.7) Eating out (≥3 times per week)	39/73 (53%)	11/20 (55%)	20/46 (44%)	10/32 (31%)
Q.8) Instant food (≥2 times per week)	32/73 (44%)*	15/20 (75%)	4/46 (9%)	4/32 (13%)
Q.9) Fast food (≥once per week)	33/73 (45%)	8/20 (40%)	18/46 (39%)	13/32 (41%)
Q.10) Canned coffee or juice (≥3 bottles per week)	14/73 (19%)	3/20 (15%)	5/46 (11%)	0/32 (0%)
Q.11) Sweets (≥0.5 times per week)	59/73 (81%)	14/20 (70%)	35/46 (76%)	24/32 (75%)
Q.12) Cakes (≥once per week)	22/73 (30%)	5/20 (25%)	16/46 (35%)	11/32 (34%)
Q.13) No regular exercise	59/73 (81%)	14/20 (70%)	35/46 (76%)	24/32 (75%)
Q.14) Elevator/escalator (prefer to use)	52/73 (71%)	14/20 (70%)	33/46 (72%)	22/32 (69%)
Q.15) Commuting method (percentage of cars)	9/73 (12%)	1/20 (5%)	1/46 (2%)	1/32 (3%)

Q, question; *p<0.05, **p<0.01.

Table 4. The comparison among non-obese groups

	Male			Female		
	Non-obese NASH	Non-obese NAFL	Non-obese control	Non-obese NASH	Non-obese NAFL	Non-obese control
Number	20	5	19	32	4	27
Age (average)	53	47	46	60	65	53.3
Ethanol (g/week) (average)	15	79.4	66.1	6	0	54.8
Brinkman index (average)	126	80	37.9	0	0	4.4
DM	6/20 (30%)	0	0	13/32 (41%)**	0	0
HT	3/20 (15%)	2/5 (40%)	2/19 (11%)	16/32 (50%)	3/4 (75%)	0
Dyslipidemia	5/20 (25%)	3/5 (60%) △	2/19 (11%)	14/32 (44%)**	2/4 (50%)	3/27 (11%)
10 kg BW gain (compare to their 20's)	7/20 (35%)*	2/5 (40%) △	1/19 (5%)	9/32 (28%)*	1/4 (25%)	1/27 (4%)
Q.1) Having breakfast everyday	11/20 (55%)	4/5 (80%)	12/19 (63%)	26/32 (81%)	4/4(100%)	22/27 (81%)
Q.2) Time required for dinner (<30 min)	12/20 (60%)	3/5 (60%)	8/19 (42%)	16/32 (50%)	2/4 (50%)	11/27 (41%)
Q.3) Rice at dinner (>1 bowl of rice)	7/20 (35%)	3/5 (60%)	4/19 (21%)	4/32 (13%)	0	0
Q.4) Meat dishes (≥3 times per week)	13/20 (65%)	3/5 (60%)	6/19 (32%)	14/32 (44%)	2/4 (50%)	20/27 (74%)
Q.5) Fries (≥3 times per week)	9/20 (45%)**	1/5 (20%) △	0	9/32 (28%)	0	4/27 (15%)
Q.6) Chinese noodles (≥3 times per week)	10/20 (50%)*	1/5 (20%)	3/19 (16%)	13/32 (41%)	1/4 (25%)	10/27 (37%)
Q.7) Eating out (≥3 times per week)	11/20 (55%)	2/5 (40%)	6/19 (32%)	10/32 (31%)	0	4/27 (15%)
Q.8) Instant food (≥2 times per week)	15/20 (75%)**	2/5 (40%)	1/19 (5%)	4/32 (13%)	0	5/27 (19%)
Q.9) Fast food (≥once per week)	8/20 (40%)	2/5 (40%)	3/19 (16%)	13/32 (41%)	0	6/27 (22%)
Q.10) Canned coffee or juice (≥3 bottles per week)	3/20 (15%)	0	2/19 (11%)	0	0	0
Q.11) Sweets (≥0.5 times per week)	14/20 (70%)	2/5 (40%)	8/19 (42%)	24/32 (75%)	2/4 (50%)	25/27 (93%)
Q.12) Cakes (≥once per week)	5/20 (25%)	0	5/19 (26%)	11/32 (34%)	2/4 (50%)	7/27 (26%)
Q.13) No regular exercise	14/20 (70%)	3/5 (60%)	9/19 (47%)	24/32 (75%)	3/4 (75%)	15/27 (56%)
Q.14) Elevator/escalator (prefer to use)	14/20 (70%)	2/5 (40%)	9/19 (47%)	22/32 (69%)	3/4(75%)	17/27 (63%)
Q.15) Commuting method (percentage of cars)	1/20 (5%)	3/6 (50%)	8/19 (42%)	1/32 (3%)	0	6/27 (22%)

Q, question; NASH vs Control *p<0.05, **p<0.01; NAFL vs Control △p<0.05, △△p<0.01. There is no difference between NASH and NAFL.

least once a week, there is a benefit for NAFLD patients.

Frequency of a proclivity for eating cakes was higher in both male and female NASH patients with severe fibrosis than in patients with mild fibrosis. The contents of dairy products, sugar, and high fat in cakes might be risk factors promoting liver fibrosis.

In this study, we compared the lifestyle of NASH to that of NAFL. The lifestyle tendencies of NAFL were almost the same as those of NASH. There are possible reasons why we could not detect a difference between NASH and NAFL. One is that some other factors, such as genomic background, might be involved. In

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fact, Tokushige[22] and Kawaguchi[17] have reported an influence of genomic background in the difference between NASH and NAFL. Another reason might be that the sample size of NAFL was too small.

In the comparison between obese NASH and non-obese NASH, no clear lifestyle differences were found. Further, Table 4 showed that even in male non-obese NASH, lifestyle was different from that in male non-obese subjects, suggesting that lifestyle plays an important role even in non-obese groups.

Samaha *et al.*[23] reported that a low-carbohydrate diet is effective against obesity and metabolic syndrome. Several studies have discussed which is more effective against obesity, a low-carbohydrate diet or a low-fat diet.[24] Although a low-carbohydrate diet induces oxidative stress, representative of the second hit of NASH, some articles have reported that a low-carbohydrate diet was effective against NASH.[25,26] It is not clear whether fats or carbohydrates are more important for the pathogenesis of NASH. Multivariate analysis showed that intake of rice, meat, and elevator use were important factors. We could not decide which, carbohydrate or fat, was more important.

When we care for NASH patients, investigation of the lifestyle of each patient is expected to suggest which points to emphasize. For example, we should recommend some or all of the following to male NASH patients: 1) When you eat dinner, take more than 30 min. 2) Limit yourself to one bowl of rice at dinner. 3) Eat only two meat dishes per week. 4) Eat fries twice or less per week. 5) Eat Chinese noodles a maximum of twice a week. 6) Eat instant food only once a week. 7) Eat as few sweets as possible. 8) Exercise regularly. 9) Use stairs as much as possible.

Toshimitsu and Cortez-Pinto[27,28] showed daily total carbohydrates, total fat and total calories in NASH patients. Although these data are scientific, the difficulty lies in the fact that patients had to guess the quantity of each nutrient from their meals. Our data are concrete, and the volume of rice and the frequencies of eating out, meat dishes, Chinese noodles, and fries are useful for the guidance and education of NASH patients. We expect that our data can be linked to therapeutic approaches, especially in male patients with NASH.

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Conflict of Interest

No potential conflicts of interest were disclosed.

References

1 Eguchi Y, Hyogo H, Ono M, *et al*. Prevalence and associated metabolic factors of nonalcoholic fatty liver disease in the general population from 2009 to 2010 in Japan: a multicenter large retrospective study. *J Gastroenterol* 2012; **47**: 586–595.
2 Teli MR, James OFW, Burt AD, Bennet MK, Day CP. The natural history of nonalcoholic fatty liver: follow-up study. *Hepatology* 1995; **22**: 1714–1719.
3 Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis; summary of an AASLD single topic conference. *Hepatology* 2003; **37**: 1202–1219.
4 Hashimoto E, Tokushige K. Hepatocellular carcinoma in non-alcoholic steatohepatitis: growing evidence of an epidemic? *Hepatol Res* 2012; **42**: 1–14.
5 Chitturo S, Abeygunasekera S, Farrell GC, *et al*. NASH and insulin resistance: insulin hypersecretion and specific association with the insulin resistance syndrome. *Hepatology* 2002; **35**: 373–379.
6 Guerra-Juárez R, Gallegos EC, Cerda-Flores RM. Lifestyle changes in descendants of parents with diabetes type 2. *Rev Lat Am Enfermagem* 2007; **15**: 909–913.
7 Pereira MA, Kartashov AI, Ebbeling CB, *et al*. Fast-food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis. *Lancet* 2005; **365**: 36–42.
8 Lau C, Faerch K, Glümer C, *et al*. Dietary glycemic index, glycemic load, fiber, simple sugars, and insulin resistance: the Inter99 study. *Diabetes Care* 2005; **28**: 1397–1403.
9 Haus JM, Solomon TP, Kelly KR, et al. Improved hepatic lipid composition following short-term exercise in nonalcoholic fatty liver disease. *J Clin Endocrinol Metab* 2013; **98**: E1181–E1188.
10 Brunt EM, Janney CG, Di Biscrglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staining the histological lesions. *Am J Gastroenterol* 1999; **94**: 2467–2474.
11 Brunt EM. Nonalcoholic steatohepatitis: definition and pathology. *Semin Liver Dis* 2001; **21**: 3–16.
12 Kleiner DE, Brunt EM, Van Natta M, *et al*. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005; **41**: 1313–1321.
13 Sumida Y, Yoneda M, Hyogo H, *et al*. A simple clinical scoring system using ferritin, fasting insulin, and type IV collagen 7S for predicting steatohepatitis in nonalcoholic fatty liver disease. *J Gastroenterol* 2011; **46**: 257–268.
14 Yatsuji S, Hashimoto E, Tobari M, Tokushige K, Shiratori K. Influence of age and gender in Japanese patients with non-alcoholic steatohepatitis. *Hepatol Res* 2007; **37**: 1034–1043.
15 Tokushige K, Hashimoto E, Noto H, *et al*. Influence of adiponectin gene polymorphisms in Japanese patients with non-alcoholic fatty liver disease. *J Gastroenterol* 2009; **44**: 976–982.
16 Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. *Hepatology* 2011; **53**: 1883–1894.
17 Kawaguchi T, Sumida Y, Umemura A, *et al*. Genetic polymorphisms of the human PNPLA3 gene are strongly associated with severity of non-alcoholic fatty liver disease in Japanese. *PLoS One* 2012; **7**: e38322.
18 Rotman Y, Koh C, Zmuda JM, Kleiner DE, Liang TJ; NASH CRN. The association of genetic variability in patatin-like phospholipase domain-containing protein 3 (PNPLA3) with histological severity of nonalcoholic fatty liver disease. *Hepatology* 2010; **52**: 894–903.
19 Hara K, Boutin P, Mori Y, *et al*. Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. *Diabetes* 2002; **51**: 536–540.
20 Yasuda K, Miyake K, Horikawa Y, *et al*. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. *Nat Genet* 2008; **40**: 1092–1097.
21 Sreenivasa Baba C, Alexander G, Kalyani B, *et al*. Effect of exercise and dietary modification on serum aminotransferase levels in patients with nonalcoholic steatohepatitis. *J Gastroenterol Hepatol* 2006; **21**: 191–198.
22 Tokushige K, Takakura M, Tsuchiya-Matsushita N, Taniai M, Hashimoto E, Shiratori K. Influence of TNF gene polymorphisms in Japanese patients with NASH and simple steatosis. *J Hepatol* 2007; **46**: 1104–1110.
23 Samaha FF, Iqbal N, Seshadri P, *et al*. A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med* 2003; **348**: 2074–2081.
24 Gill HK, Wu GY. Non-alcoholic fatty liver disease and the metabolic syndrome: effects of weight loss and a review of popular diets. Are low carbohydrate diets the answer? *World J Gastroenterol* 2006; **12**: 345–353.
25 York LW, Puthalapattu S, Wu GY. Nonalcoholic fatty liver disease and low-carbohydrate diets. *Annu Rev Nutr* 2009; **29**: 365–379.
26 Tendler D, Lin S, Yancy WS Jr., *et al*. The effect of a low-carbohydrate, ketogenic diet on nonalcoholic fatty liver disease: a pilot study. *Dig Dis Sci* 2007; **52**: 589–593.
27 Toshimitsu K, Matsuura B, Ohkubo I, *et al*. Dietary habits and nutrient intake in non-alcoholic steatohepatitis. *Nutrition* 2007; **23**: 46–52.
28 Cortez-Pinto H, Jesus L, Barros H, Lopes C, Moura MC, Camilo ME. How different is the dietary pattern in non-alcoholic steatohepatitis patients? *Clin Nutr* 2006; **25**: 816–823.