Original Article

Comparisons of dietary intake in Japanese with non-alcoholic fatty liver disease and type 2 diabetes mellitus

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Non-alcoholic fatty liver disease (NAFLD) is a multifactorial disease that involves a complex interaction between genetics, diet, and lifestyle, all of which combine to form the NAFLD phenotype. In Japan, medical nutrition therapy for NAFLD has not yet been established, so NAFLD patients are instructed in the dietary modifications used for type 2 diabetes mellitus (T2DM). Because points of difference may exist in the effects of dietary choices on NAFLD and T2DM, the present study aimed to compare and assess the dietary intake of Japanese individuals with NAFLD and T2DM. This cross-sectional study involved 219 patients (77 NAFLD subjects; 33 males, 44 females; 142 T2DM subjects: 76 males, 66 females) aged 40–79 years. Dietary intake was assessed using a validated self-administered diet history questionnaire. Among the results, the most notable in NAFLD patients relative to T2DM patients were: 1) the low intake of vegetables that can reduce the overall energy density; 2) the high consumption of fruits and confectionery containing simple carbohydrates such as fructose; and 3) BMI may be higher. We demonstrated differences in dietary selection between the two groups. NAFLD patients were more likely to have dietary habits that promote fat accumulation in the body.

Key Words: **non-alcoholic fatty liver disease, diabetes mellitus, dietary intake, dietary habits, vegetables, fructose**

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in many developed countries, representing a serious public health problem worldwide.[1–3] According to a cooperative study group, the Japan Study Group of NAFLD (JSG-NAFLD), 29.7% of health checkup examinees had NAFLD.[4,5] The earliest manifestation of NAFLD is hepatic steatosis, which is an excessive accumulation of triglycerides within hepatocytes. Hepatic steatosis is characterized by insulin resistance, components of metabolic syndrome, a high visceral adipose tissue content and an elevated risk of type 2 diabetes mellitus (T2DM).[6] On the other hand, the prevalence of T2DM has been increasing around the world,[7] including Japan. The number of Japanese patients with diabetes or in a pre-diabetic state (hemoglobin (Hb)A1c≥5.5%) is estimated to be about 20.5 million, representing an increase of about 4.3 million over the 10-year period ending in 2012.[8] The incidence of T2DM is a result of a progressive defect in insulin secretion due to insulin resistance.[9] Given this common background of overweight status and/or metabolic syndrome associated with the development of NAFLD and T2DM, the influence of dietary habits is expected to be large.

Medical nutrition therapy for the management of diabetes plays an important role in preventing complications associated with diabetes, particularly in the management of metabolic control and optimal weight.[10,11] On the other hand, NAFLD is a multifactorial disease that involves a complex interaction between genetics, diet, and lifestyle, all of which combine to form the NAFLD phenotype. The only established treatment for NAFLD is the use of diet and lifestyle changes to decrease body weight and improve glycemic control, dyslipidemia, and cardiovascular risk.[12–15] In Japan, medical nutrition therapy for NAFLD has not yet been established, so NAFLD patients are instructed in the dietary modifications used for T2DM. If points of difference exist in the effects of dietary choices on NAFLD and T2DM, the nutritional instructions provided to patients with NAFLD will need to be amended. However, few reports have compared the feature of these two diseases in terms of the dietary habits of patients, especially in Japan. This study aimed to compare and assess the dietary intake of Japanese individuals with NAFLD and T2DM, to optimize the dietary instructions for NAFLD.

Materials and Methods

Subjects. This study enrolled NAFLD subjects receiving treatment in Nara City Hospital (Nara, Japan) and T2DM subjects being treated in University Hospital, Kyoto Prefectural University of Medicine (Kyoto, Japan). NAFLD was diagnosed on the basis of liver biopsy (performed according to clinical judgment) and a patient report of alcohol intake <30 g/day for males and <20 g/day for females.[16] A self-administered diet history questionnaire (DHQ) was given to 381 subjects. A total of 325 subjects completed the questionnaire, yielding a collection rate of 85.3%. A total of 219 subjects (77 NAFLD subjects; 33 males, 44 females; 142 T2DM subjects: 76 males, 66 females) met the inclusion criteria, after applying the following exclusion criteria: age <40 years or ≥80 years; presence of chronic renal failure or hemodialysis; incomplete information; or subjects in the ≥95th or ≤5th percentile for energy intake. Data were collected from June 2011 to February 2013. Each subject agreed to participate in the study by signing an informed consent form prior to enrolment. The experimental protocol was approved by the ethics committees of Kyoto Prefectural University of Medicine, Nara City Hospital, and Kyoto Prefectural University (Kyoto, Japan).

Assessment of habitual food and nutrient intake. The usual dietary habits of participants during the 1-month period preceding the study were assessed with the validated DHQ

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system.[17] The questionnaire employed in this system consists of questions regarding general dietary behavior, major cooking methods, the quantity and frequency of consuming 149 selected food and beverage items, and the amount of rice and miso soup consumed daily. Food and beverage items and portion sizes in the questionnaire were derived primarily from data in the National Nutrition Survey of Japan[18] and several recipe books for Japanese dishes. We determined the intake of each food group (grains and cereals, potatoes, sugar, pulses, nuts, total vegetables, green vegetables, white vegetables, fruits, mushrooms, algae, fish and shellfishes, meat, eggs, milk, oils and fats, and confectionery), total energy intake, percentage of energy from protein, fat, and carbohydrates (without alcoholic), and the intake of each of the following nutrients: saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid, cholesterol, fiber, alcoholic, vitamins A, D, E, K, B_1, B_2, B_6, B_{12}, C, niacin, folic acid, pantothenic acid, sodium, potassium, calcium, magnesium, phosphorus, iron, zinc, and copper. These intakes were inputted using a dedicated program for the DHQ system (DHQ BOX system 2013; Gender Medical Research, Tokyo, Japan). Intake values obtained from the analysis were adjusted to the amount per 1,000 kcal of intake.

Physical status and blood constituent values of subjects. Data on physical status and blood constituent values of the subjects were taken from the electronic medical records. Regarding physical status and medication, we obtained the following data: age, height, body weight, and body mass index (BMI). Blood constituent values of participants were obtained for the following items: HbA1c (NAFLD group, $n = 53$; T2DM group, $n = 142$), aspartate aminotransferase (AST, NAFLD group, $n = 77$; T2DM group, $n = 141$), and alanine aminotransferase (ALT, NAFLD group, $n = 77$; T2DM group, $n = 141$).

Statistical analysis. Data are presented as mean ± SD. Relationships between NAFLD and T2DM were assessed according to physical status, energy intake, blood constituent values (Table 1), intake of food groups (Table 2), and intake of nutrients (Table 3) using the Mann-Whitney *U* test. All analyses were performed with SPSS Statistics ver. 22.0 (IBM, Chicago, IL). The level of significance was set at $p<0.05$.

Results

Characteristics. Data on physical status, energy intake, and blood constituent values of subjects are shown in Table 1. Significant differences were demonstrated between NAFLD and T2DM groups for BMI, HbA1c, AST and ALT. However, no significant differences were demonstrated between age and energy intake [kcal/kg ideal body weight (IBW)]. BMI was significantly higher in the NAFLD group (26.9 ± 4.8 kg/m^2) than in the T2DM group (24.0 ± 4.2 kg/m^2, $p<0.001$). HbA1c was significantly lower in the

Table 1. Charastaristics of non-alcoholic fatty liver disease (NAFLD) and type 2 diabetic mellitus (T2DM) patients

	NAFLD group *n* = 77	T2DM group *n* = 142	*p* value
Sex (Male/Female)	33/44	76/66	—
Age (years)	62.5 ± 9.7	64.9 ± 8.8	0.083
BMI (kg/m^2)	26.9 ± 4.8	24.0 ± 4.2	<0.001
Energy intake (kcal/kg IBW*)	34.1 ± 9.0	31.9 ± 7.0	0.111
HbA1c (%)	6.2 ± 0.7	6.8 ± 0.9	<0.001
AST** (IU/L)	41 ± 20	25 ± 10	<0.001
ALT*** (IU/L)	55 ± 36	24 ± 15	<0.001

Values were represented as means ± SD. Relationships between the NAFLD and T2DM groups were evaluated using the Mann-Whitney *U* test. *IBW, ideal body weight. **AST, aspartate aminotransferase. ***ALT, aranine aminotransferase.

Table 2. Comparisons between NAFLD and T2DM in the intake of food groups (g/1,000 kcal/day)

	NAFLD *n* = 77	T2DM *n* = 142	*p* value
Grains and Cereals	173 ± 68	198 ± 70	0.003
Potatoes	10 ± 10	13 ± 14	0.092
Sugar	6 ± 4	6 ± 4	0.625
Pulses	30 ± 43	26 ± 24	0.900
Nuts	1.6 ± 4.0	1.4 ± 3.2	0.836
Vegetables	123 ± 89	148 ± 119	0.212
Green vegetables	74 ± 71	70 ± 78	0.979
White vegetables	49 ± 29	78 ± 58	<0.001
Fruits	86 ± 86	53 ± 45	0.030
Mushrooms	4 ± 5	6 ± 8	0.042
Algae	4 ± 6	5 ± 7	0.057
Fish and shellfishes	35 ± 22	40 ± 23	0.026
Meats	26 ± 20	27 ± 20	0.936
Eggs	13 ± 11	19 ± 25	0.006
Milk	69 ± 55	67 ± 54	0.788
Oil and fats	9 ± 8	9 ± 6	0.375
Confectionery	35 ± 28	28 ± 26	0.027

Values were represented as means ± SD. Relationships between the NAFLD and T2DM groups were evaluated using the Mann-Whitney *U* test.

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Table 3. Comparisons of nutrient intakes between NAFLD and T2DM (per day)

	NAFLD *n* = 77	T2DM *n* = 142	*p* value
Energy ratio of Protein (E%)	14.3 ± 2.3	13.3 ± 3.6	0.008
Energy ratio of Fat (E%)	26.8 ± 6.7	25.9 ± 6.7	0.265
Energy ratio of Carbohydrate* (E%)	58.6 ± 8.1	57.4 ± 9.6	0.397
Saturated fatty acid (g/1,000 kal)	7.1 ± 3.2	7.3 ± 3.0	0.560
Monounsaturated fatty acid (g/1,000 kcal)	9.0 ± 4.2	9.1 ± 3.8	0.885
Polyunsaturated fatty acid			
n-3 (g/1,000 kcal)	1.1 ± 0.6	1.2 ± 0.5	0.179
n-6 (g/1,000 kcal)	4.7 ± 2.2	4.9 ± 1.9	0.514
Cholesterol (mg/1,000 kcal)	133 ± 67	152 ± 66	0.025
Fiber (g/1,000 kcal)	5.8 ± 2.5	6.7 ± 2.9	0.016
Alcoholic (g/1,000 kcal)	0.4 ± 1.1	4.6 ± 10.5	<0.001
Vitamin A (μg/1,000 kcal)	263 ± 229	263 ± 154	0.267
Vitamin B_1 (mg/1,000 kcal)	0.4 ± 0.1	0.4 ± 0.1	0.644
Vitamin B_2 (mg/1,000 kcal)	0.6 ± 0.2	0.7 ± 0.2	0.020
Niacin (mg/1,000 kcal)	7.3 ± 3.0	8.3 ± 2.8	0.003
VitaminB_6 (mg/1,000 kcal)	0.6 ± 0.3	0.6 ± 0.2	0.168
Vitamin B_{12} (μg/1,000 kcal)	3.2 ± 1.7	3.6 ± 1.8	0.023
Folic acid (μg/1,000 kcal)	136 ± 57	159 ± 63	0.004
Pantothenic acid (mg/1,000 kcal)	2.8 ± 1.2	2.9 ± 0.8	0.091
Vitamin C (mg/1,000 kcal)	49 ± 31	52 ± 27	0.222
Vitamin D (μg/1,000 kcal)	3.9 ± 2.5	4.5 ± 2.3	0.020
Vitamin E (mg/1,000 kcal)	3.9 ± 1.8	4.0 ± 1.6	0.483
Vitamin K (μg/1,000 kcal)	103 ± 84	125 ± 84	0.007
Natrium (mg/1,000 kcal)	1,817 ± 686	2,052 ± 679	0.008
Potassium (mg/1,000 kcal)	1,164 ± 466	1,205 ± 420	0.222
Phosphorus (mg/1,000 kcal)	462 ± 146	503 ± 141	0.020
Calcium (mg/1,000 kcal)	242 ± 90	260 ± 101	0.228
Magnesium (mg/1,000 kcal)	119 ± 42	127 ± 40	0.058
Iron (mg/1,000 kcal)	3.2 ± 1.3	3.5 ± 1.2	0.018
Zinc (mg/1,000 kcal)	3.4 ± 1.0	3.7 ± 1.0	0.028
Copper (mg/1,000 kcal)	0.5 ± 0.2	0.5 ± 0.2	0.068

Values were represented as means ± SD. Relationships between the NAFLD and T2DM groups were evaluated using the Mann-Whitney *U* test. *without alcoholic.

NAFLD group than in the T2DM group (p<0.001). AST and ALT were significantly higher in the NAFLD group than in the T2DM group (p<0.001 and p<0.001, respectively).

Comparisons between NAFLD and T2DM for intake of food groups. Table 2 shows comparisons between NAFLD and T2DM in the intake of food groups. The food groups showing significantly higher intakes in NAFLD than in T2DM were confectionery ($p = 0.027$) and fruits ($p = 0.030$). On the other hand, intake of white vegetables, mushrooms, eggs, fish and shellfish, and grains and cereals was significantly lower in NAFLD compared with T2DM. Total vegetable intake tended to be lower in NAFLD than in T2DM, but this difference was not significant.

Comparisons between NAFLD and T2DM for nutrient intake. Comparisons of nutrient intakes between patients with NAFLD and T2DM are shown in Table 3. Nutrient intakes showing significantly lower values in NAFLD than in T2DM were cholesterol, fiber, vitamin B_2, niacin, vitamin B_{12}, folic acid, vitamin D, vitamin K, sodium, phosphorus, iron, zinc and alcohol. No nutrients showed significantly higher intakes in NAFLD compared with T2DM. However, a significantly higher energy ratio from protein was seen in NAFLD than in T2DM ($p = 0.008$).

Discussion

The present study examined self-reported habitual food and nutrient intakes for Japanese patients to compare NAFLD and T2DM. Our results provide new evidence suggesting that BMI may be higher in NAFLD than in T2DM, and differences in dietary selection are seen between patients with these pathologies. Among the results, the most notable in NAFLD patients relative to T2DM patients were: 1) the low intake of vegetables; and 2) the high consumption of fruits and confectionery.

The first issue of note was the low intake of vegetables in NAFLD patients compared with T2DM patients. Although the intake of green vegetables tended to be higher, intake of white vegetables was significantly lower in individuals with NAFLD compared with T2DM. One reason for this result may be that patients with T2DM received better education about suitable intakes of vegetables compared to NAFLD. We did not examine the patients' dietary education records in this research. However, we presume NAFLD patients at most received a guidance on dietary balances. This is because dietary education method for NAFLD patients has not been established yet. In contrast, dietary education method for T2DM has been established using the Food Exchange Lists compiled by the Japanese Diabetes Society. According to the list, appropriate vegetable intake is 360 g/day.

On the other hand, the intake of vegetables in T2DM was not necessarily high, because a previous study found a low intake of vegetables in Japanese patients with T2DM compared with the national average.[19] These findings suggest that vegetable intakes in patients with NAFLD would be markedly below the Japanese average. NAFLD patients have thus been assumed to have a lifestyle with a very low intake of vegetables. Although the relationship between vegetable intake and NAFLD is unclear, vegetables contain nutrients such as antioxidants, and improved intake may help improve the pathogenesis of NAFLD. For example, vitamin E is known to affect free-radical reactions, such as lipid peroxidation, which are thought to act on transforming growth factor (TGF)-β1, peroxisome proliferator-activated receptors, and apoptosis-regulating genes.[20,21] In recommendations published in 2014, the guidelines edited by the Japanese Society of Gastroenterology reported that vitamin E improves hepatic biological and histological parameters in patients with NASH and recommended this therapy for NASH patients, as evidence level A.[16] On the other hand, body weight reduction has been reported to improve liver function and fatty changes in the liver in patients with NAFLD.[22,23] Several studies have shown that lowering the energy density of foods enhances satiation,[24–28] and vegetables generally have a high water content and low energy density. Dietary vegetables can thus reduce the overall energy density and allow consumption of satisfying portions while reducing calorie intake, and this strategy could play an important role in weight management.[29] We therefore cannot overlook the point that vegetable intake was lower in NAFLD than in T2DM in the present study. This will likely lead to proposals for new dietary therapies addressing this point. In addition, several cohort studies have shown that a sufficient intake of vegetables reduced the risk of developing diabetes,[30,31] and a diet high in dietary fiber-containing vegetables might improve glycemic control.[32,33] Improved vegetable intake might thus prevent the progression of NAFLD, and nutritional education to strengthen vegetable intake may prove beneficial for NAFLD patients.

Second, NAFLD patients showed significantly higher consumption of confectionery and fruit compared with T2DM patients. Particular attention must be paid to the intake of such foods, as fructose in large amounts readily leads to excess energy consumption. Toshimitsu *et al.*[34] reported that intake of sweets containing simple carbohydrates, such as fructose, was higher among Japanese individuals with NASH.[34] Our results are in agreement with that report. Stanhope *et al.*[35] reported that consumption of fructose-sweetened beverages to provide 25% of the energy intake for 10 weeks increased *de novo* lipogenesis, promoted dyslipidemia, decreased insulin sensitivity, and increased visceral adiposity in overweight/obese individuals, whereas consumption of a comparable amount of glucose-sweetened beverages did not.[35] Fructose is metabolized primarily in the liver, and uptake by the liver rapidly decreases ATP as the phosphate is transferred to fructose in a form that facilitates conversion to lipid precursors. Fructose intake enhances lipogenesis and the production of uric acid. By worsening blood lipid levels, contributing to obesity, diabetes, fatty liver, and gout, fructose in the amounts currently consumed is hazardous to the health of some individuals.[36–38] Assessing whether excessive levels of fructose were consumed in this study is difficult, but one factor contributing to the higher BMI in NAFLD patients compared with T2DM patients may be that NAFLD patients show dietary selections and habits that facilitate the accumulation of visceral fat. Moreover, there were no significant differences in energy ratio of carbohydrate between the NAFLD and T2DM groups although NAFLD patients showed significantly higher consumption of confectionery and fruit compared with T2DM patients. We assume that these results were ascribed to be significantly lower intake of grains and cereals in NAFLD than T2DM.

We also found that intakes of many vitamins, especially from the vitamin B group, and minerals were lower with NAFLD than with T2DM. This is presumably attributable to the lower intake of fish and eggs by the NAFLD group compared with the T2DM group, but no clear relationship was apparent in this study.

Several limitations must be considered when interpreting the present results. We speculated that some selection bias may have been present, as these patients self-selected to participate in the study. The energy intake obtained by the dietary assessment has a tendency to represent an underestimation. As this study was conducted within the context of a hospital where the patient received treatment, they may have under-reported the intake of less desirable foods and over-reported the intake of healthier foods in order to satisfy the researchers. In addition, NAFLD patients may have been included among T2DM patients, because the T2DM patients did not undergo liver biopsy. Similarly, T2DM patients may have been included among NAFLD patients by complication. Further research is required to investigate the dietary intake of NAFLD without T2DM and T2DM without NAFLD, but no clear relationship was apparent in this study.

We assessed the dietary intakes of Japanese patients with NAFLD and T2DM and demonstrated differences in dietary selection between the two groups. NAFLD patients were more likely to have dietary habits that promote fat accumulation in the body, such as a relatively lower intake of vegetables and higher intakes of sweets and/or fruit, compared to T2DM patients. In the future, an understanding of such lifestyle factors would seem prudent when implementing dietary instruction for patients with NAFLD. These features will likely be incorporated in the data pool for dietary therapy and nutritional education, and therapeutic guidance for Japanese NAFLD patients should reflect these results in the future.

Authors' Contribution

Designed the experiments: YKo and YKi, Performed the experiments: YKo, HT, MH, ST, KK, YS and MF, analysis: YKo, HT, MH and HS, interpretation of date: YKo, SW, MK, YS, YN, MF and YKi, preparation of manuscript: YKo. All authors read and approved the final manuscript.

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Conflicts of Interest

No potential conflicts of interest were disclosed.

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