The Association of Salt Intake and Non-alcoholic Fatty Liver Disease in People With Type 2 Diabetes: A Cross-Sectional Study

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Objectives: Non-alcoholic fatty liver disease (NAFLD), which has a close relationship with type 2 diabetes (T2D), is related to salt intake in the general population. In contrast, the relationship between salt intake and the presence of NAFLD in patients with T2D has not been clarified.

Methods: Salt intake (g/day) was assessed using urinary sodium excretion, and a high salt intake was defined as an intake greater than the median amount of 9.5 g/day. Hepatic steatosis index (HSI) ≥ 36 points was used to diagnosed NAFLD. Odds ratios of high salt intake to the presence of NAFLD were evaluated by logistic regression analysis.

Results: The frequency of NAFLD was 36.5% in 310 patients with T2D (66.7 ± 10.7 years old and 148 men). The patients with high salt intake had a higher body mass index (25.0 ± 4.0 vs. 23.4 ± 3.8 kg/m², p < 0.001) than those with low salt intake. HSI in patients with high salt intake was higher than that in patients with low salt intake (36.2 ± 6.2 vs. 34.3 ± 5.5 points, p = 0.005). In addition, the presence of NALFD in patients with high salt intake was higher than that in patients with low salt intake (44.5% vs. 28.4%, p = 0.005). High salt intake was associated with the prevalence of NAFLD [adjusted odds ratio, 1.76 (95% confidence interval: 1.02–3.03), p = 0.043].

Conclusion: This cross-sectional study revealed that salt intake is related to the prevalence of NAFLD in patients with T2D.

Keywords: salt intake, diet, NAFLD, type 2 diabetes, nutrition

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is associated with chronic liver disease (1). NAFLD is regarded as the hepatic phenotype of ectopic accumulation of fat due to abdominal obesity and insulin resistance, and its existence relates to the accumulation of fat in visceral, perivascular, epicardial, and intramuscular tissues (2, 3). Patients with type 2 diabetes (T2D) often suffer from NAFLD (3). The presence of NAFLD is especially high in people with obesity and/or T2D, and it has
been found that NAFLD is present in approximately 50–60% of patients with T2D (4, 5). Preexisting diabetes was increasing the risk of NAFLD and death related to the liver in prospective studies (6, 7). Therefore, NAFLD in patients with T2D deserves more caution than in people without diabetes.

Lifestyle, including dietary habits, affects to NAFLD development. Excess energy intake increases hepatic fat mass (4), and eating fast has been related to the prevalence of NAFLD in patients with T2D (8). Moreover, an association between salt intake and NAFLD in the general population has been reported (9, 10). High salt intake raises blood pressure and increases the risk factor for cardiovascular disease (CVD) (11, 12). Furthermore, the relationship between high salt intake and a risk of obesity were shown in previous studies (13–17). High salt intake has been established as a risk of metabolic disorders (18–21). However, the association between salt intake and NAFLD in patients with T2D has not been clarified yet. Thus, this cross-sectional study intended to reveal the correlation between salt intake and NAFLD in patients with T2D.

MATERIALS AND METHODS
Study Participants
Since 2014, we have been conducting a prospective cohort study, the KAMOGAWA-DM cohort study, which aims to identify the natural history of people with diabetes (22). In the present study, we enrolled outpatients of the Department of Endocrinology and Metabolism at Kyoto Prefectural University of Medicine (KPUM) Hospital (Kyoto, Japan) or the Department of Diabetology at Kameoka Municipal Hospital (Kameoka, Japan) who completed questionnaires between January 2016 and December 2018. This study excluded people with the following characteristics: non-T2D, absent data on hepatic steatosis index (HSI), viral hepatitis, liver cancer, alcohol consumption ≥ 20 g/day (23), absent data on urinary creatinine (Cr) and sodium (Na), and incomplete questionnaires. The approve of present study was obtained from the ethics committee of KPUM (No. RBMR-E-466-6) and this study was executed according to the Declaration of Helsinki. Written informed consent was provided from all participants.

Data Collection
Smoking status and physical activity were assessed by questionnaires. “Habit of smoking” was defined as smoking cigarettes or another tobacco product currently. “Habit of exercise” was defined as an engagement in any type of exercise once a week or more. Additionally, all participants were questioned about the duration of their diabetes. Venous blood was gathered after fasting all night and checked for the following factors: plasma glucose, glycosylated hemoglobin (HbA1c), triglycerides, high-density lipoprotein cholesterol, gamma-glutamyl transpeptidase (γ-GTP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine (Cr). Estimated glomerular filtration rate (eGFR) was calculated as $194 \times \text{age}^{-0.287} \times \text{Cr}^{-1.094}$ (if women, $\times 0.739$) (mL/min/1.73 m²) as defined by the Japanese Society of Nephrology (24).

Body mass index (BMI) was evaluated by dividing body weight (kg) by height² (m²). Ideal body weight (IBW) was calculated as $22 \times \text{(square of the participant’s height [m²])}$ (25). In addition, data on medications, including antidiabetic and antihypertensive drugs, were gathered from patients’ records. Blood pressure was tested automatically using an HEM-906 device (OMRON, Kyoto, Japan) in a sitting posture after 5 min of rest in a quiet room. Hypertension was defined as the use of antihypertensive drugs, systolic blood pressure ≥ 140 mmHg, and/or diastolic pressure ≥ 90 mmHg (26).
Questionnaire for Dietary Habit

We evaluated the participants’ habitual food and nutrient intake during the previous 1 month using a brief-type self-administered diet history questionnaire (BDHQ). The validity and detail of the BDHQ have been shown previously (27). Energy intake (kcal/day), protein intake (g/day), carbohydrate intake (g/day), fat intake (g/day), alcohol consumption (g/day) and fiber intake (g/day) were assessed using the BDHQ. Furthermore, energy (kcal/IBW/day), protein (g/IBW/day), carbohydrate (g/IBW/day), fat (g/IBW/day) intakes were estimated by each intake divided by IBW.

Definition of Salt Intake

The patients supplied samples of urine from their second early morning urination. Urinalysis was performed to assess densities of Cr (mg/dL) and Na (mg/dL). We estimated the 24h salt intake with the Tanaka formula (28, 29): Estimated 24h salt intake (g/day) = 21.98 × (urinary Na (mg/dL)/urinary Cr/ 10 × (−2.043 × age + 14.89 × body weight (kg) + 16.14 × height (cm) −2244.5)∧0.392)/17.

Patients with high salt intake were defined as those consuming more than the median intake of 9.5 g/day.

Definition of NAFLD

Patients who consumed alcohol were excluded from the study. HSI (30), which is calculated using the ALT/AST ratio, sex, BMI, and impaired fasting glucose (defined as blood glucose levels >110 mg/dL) was utilized for the prevalence of fatty liver. The formula for HSI was as follows: HSI = 8 × (ALT/AST) + BMI [+2, if impaired fasting glucose (all of the participants in the present study); +2, if women]. Patients having NAFLD were defined as those with a HSI score ≥36 points.

Statistical Analysis

Data are shown as a mean ± standard deviation (SD) or frequencies of potential confounding variables. Patients were divided into two groups according to their salt intake. The differences in the categorical and continuous variables were assessed by the Student’s t-test and chi-square test, respectively.

Logistic regression analyses were performed to investigate the association between having NAFLD and taking high salt intake. The independent variables were age, HbA1c, sodium glucose cotransporter-2 inhibitor, insulin treatment, glucagon-like peptide-1 receptor agonist, duration of diabetes, exercise, smoking, energy and dietary fiber intake.

Statistical significance was set at p < 0.05. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (31).

RESULTS

The present study included 425 patients. We excluded 115 patients: 35 patients were not T2D, one patient had liver cancer, 10 patients had viral hepatitis, 2 patients had unknown liver disease, 21 patients did not complete questionnaires, 42 patients had the habit of drinking alcohol, 3 patients did not have urinary data, and one patient did not calculate HSI due to lack of data; thus, the final study population consisted of 310 patients (148 men and 162 women) (Figure 1).

The characteristics of the study participants are indicated in Table 1. Mean age and BMI were 66.7 ± 10.7 years, and 24.2 ± 4.0 kg/m², respectively. Mean HSI was 35.3 ± 5.9 points and the percentage of patients with NAFLD was 36.5%. In addition, the mean salt intake was 9.4 ± 2.5 g/day.

The characteristics of the patients according to salt intake are indicated in Table 2. The patients with high salt intake...
TABLE 2 | Clinical characteristics according to salt intake.

|                         | Estimated salt intake (low) | Estimated salt intake (high) | \( P \) |
|-------------------------|-----------------------------|------------------------------|--------|
| Age (years)             | 68.6 (10.2)                 | 64.9 (10.9)                  | 0.002  |
| Sex (men/women)         | 73 [47.1%] / 82 [52.9%]     | 75 [48.4%] / 80 [51.6%]     | 0.909  |
| Duration of diabetes (years) | 15.0 (10.8)                  | 13.4 (9.2)                   | 0.159  |
| Family history of diabetes (-/+) | 80 [51.6%] / 75 [48.4%] | 92 [59.4%] / 63 [40.6%]     | 0.209  |
| Body mass index (kg/m\(^2\)) | 23.4 (3.8)                  | 25.0 (4.0)                   | <0.001 |
| Systolic blood pressure (mmHg) | 133.7 (17.9)               | 133.2 (17.8)                 | 0.814  |
| Diastolic blood pressure (mmHg) | 77.4 (11.6)                 | 79.4 (10.6)                  | 0.119  |
| Antihypertensive drugs (-/+) | 73 [47.1%] / 82 [52.9%]     | 75 [48.4%] / 80 [51.6%]     | 0.909  |
| Presence of hypertension (-/+) | 75 [48.4%] / 80 [51.6%]     | 74 [47.7%] / 81 [52.3%]     | 1.000  |
| Insulin (-/+)           | 121 [78.1%] / 34 [21.9%]    | 117 [75.5%] / 38 [24.5%]    | 0.687  |
| SGLT2 inhibitor (-/+)    | 135 [87.1%] / 20 [12.9%]    | 124 [80.0%] / 31 [20.0%]    | 0.126  |
| GLP-1 receptor agonist (-/+) | 134 [86.5%] / 21 [13.5%]    | 125 [80.6%] / 30 [19.4%]    | 0.220  |
| Habit of smoking (-/+)  | 140 [90.3%] / 15 [9.7%]     | 133 [85.8%] / 22 [14.2%]    | 0.293  |
| Habit of exercise (-/+) | 82 [52.9%] / 73 [47.1%]     | 73 [47.1%] / 82 [52.9%]     | 0.363  |
| HbA1c (mmol/mol)        | 7.3 (1.3)                   | 7.3 (1.2)                    | 0.766  |
| HbA1c (%)               | 56.7 (13.7)                 | 56.3 (13.4)                  | 0.766  |
| Creatinine (umol/L)     | 74.0 (36.3)                 | 69.4 (23.9)                  | 0.183  |
| eGFR (mL/min/1.73 m\(^2\)) | 67.2 (18.1)                | 72.0 (19.9)                  | 0.025  |
| Triglycerides (mmol/L)  | 1.4 (0.9)                   | 1.5 (0.8)                    | 0.100  |
| HDL cholesterol (mmol/L) | 1.6 (0.4)                   | 1.5 (0.4)                    | 0.053  |
| Aspartate aminotransferase (IU/L) | 23.2 (10.4)             | 22.5 (8.7)                   | 0.501  |
| Alamine aminotransferase (IU/L) | 23.2 (14.8)             | 23.4 (14.3)                  | 0.894  |
| Gamma-glutamyl transferase (IU/L) | 33.7 (38.4)        | 31.7 (24.1)                  | 0.587  |
| HSI (point)             | 34.3 (5.5)                  | 36.2 (6.2)                   | 0.005  |
| Presence of NAFLD (-/+) | 111 [71.6%] / 44 [28.4%]    | 86 [55.5%] / 69 [44.5%]      | 0.005  |
| Urinary Creatinine (umol/L) | 114.2 (61.3)             | 60.7 (33.9)                  | <0.001 |
| Urinary Na (umol/L)     | 87.5 (38.4)                 | 120.6 (49.7)                 | <0.001 |
| Salt intake (g/day)     | 7.4 (1.4)                   | 11.3 (1.8)                   | <0.001 |
| Total energy intake (kcal/day) | 1,657.9 (563.0)            | 1,691.0 (564.6)              | 0.605  |
| Energy intake (kcal/IBW/day) | 29.9 (10.2)             | 29.7 (9.8)                   | 0.877  |
| Total protein intake (g/day) | 72.3 (29.4)             | 70.3 (26.3)                  | 0.531  |
| Protein intake (g/IBW/day) | 1.3 (0.6)       | 1.2 (0.5)                    | 0.223  |
| Total fat intake (g/day) | 54.3 (24.0)                 | 54.2 (19.6)                  | 0.984  |
| Fat intake (g/IBW/day)   | 1.0 (0.4)                   | 1.0 (0.4)                    | 0.593  |
| Total carbohydrate intake (g/day) | 212.4 (75.2)        | 223.4 (88.1)                 | 0.236  |
| Carbohydrate intake (g/IBW/day) | 3.8 (1.3)          | 3.9 (1.5)                    | 0.552  |
| Dietary fiber intake (g/day) | 12.3 (4.8)             | 12.3 (6.2)                   | 0.892  |
| Carbohydrate-to-dietary fiber intake ratio | 18.6 (6.5)   | 19.3 (7.1)                   | 0.337  |

Data were expressed as mean (standard deviation) or number [%]. The difference between group was evaluated by Student’s t-test or chi-square test. eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HDL, high-density lipoprotein; HSI, hepatic steatosis index; SGLT2, sodium glucose cotransporter-2.

were younger (64.9 ± 10.9 vs. 68.6 ± 10.2 years, \( p = 0.002 \)) and had a higher BMI (25.0 ± 4.0 vs. 23.4 ± 3.8 kg/m\(^2\), \( p < 0.001 \)) than those with low salt intake. HSI in patients with high salt intake was higher than that in patients with low salt intake (36.2 ± 6.2 vs. 34.3 ± 5.5 points, \( p = 0.005 \)). The presence of NAFLD in patients with high salt intake was higher than that in patients with low salt intake (44.5% vs. 28.4%, \( p = 0.005 \)).

The association between salt intake and the prevalence of NAFLD is shown in Table 3. High salt intake was related to the presence of NAFLD [adjusted odds ratio, 1.76 (95% confidence interval: 1.02–3.03), \( p = 0.043 \)].

DISCUSSION

This is the initial study to clarify the relationship between salt intake and the prevalence of NAFLD in patients with T2D. The findings of the present study indicated that high salt intake is related to the presence of NAFLD in patients with T2D.
There are several possible interactions between high salt intake and NAFLD. NAFLD is regarded as the hepatic element of metabolic syndrome, with inordinate accumulation of fat and insulin resistance acting functioning as the major contributors in its pathophysiology (32, 33). High salt intake is known to induce insulin resistance (34) and white adipose tissue mass (13, 15, 35). The present study indicates that high salt intake might be associated with the presence of NAFLD because it promotes insulin resistance and fat accumulation. Previous studies have found that a high salt intake is associated with NAFLD in the general population (9, 10). Additionally, animal studies have revealed that high salt diet decreases the liver's antioxidant defenses (36) and may promote inflammation and fibrosis in liver (37). In a previous study, high salt intake led to an increase in the sodium levels in liver tissue whereas it was accompanied by a decline in mitochondrial respiratory activity (38). Mitochondrial dysfunction enhances hepatocyte steatosis (38). Moreover, recent experimental studies have shown that high salt intake induces leptin resistance via activating the aldose reductase–fructokinase pathway, production of endogenous fructose and increased white adipose tissue mass via leptin production and adipocyte hypertrophy in the liver (14, 35, 39). Leptin resistance leads to fatty liver (14). Animal studies have revealed that leptin prevents ectopic fat accumulation and lipotoxicity (40). Leptin resistance might facilitate the accumulating fat in the liver and explain the occurrence of hepatic steatosis. The relationship between leptin resistance and NAFLD has been reported in patients with T2D (41).

This study had some limitations. First, salt intake was not accurately measured. Although the Na excretion, which was estimated using the aforementioned formula, has been reported to correlate with the measured 24 h Na excretion \( r = 0.54, p < 0.01 \) (29), a previous study showed that data from the Tanaka formula are underestimated when excretion is low and are overestimated when excretion is high (42). Thus, to accurately assess salt intake, multiple sampling of 24 h urinary collections were necessary. Second, plasma leptin levels were not included. Therefore, the causal association between salt intake, leptin levels, and NAFLD is not clear. Third, the results of BDHQ reflect the previous month’s dietary habits. Thus, it is possible that the results of BDHQ may not reflect the content of food intake when estimating the 24 h salt intake using the Tanaka formula. Fourth, due to the cross-sectional nature of this study, it was impossible to exhibit a causal association. We need further research, such as conducting a longitudinal study. Furthermore, previous studies have showed that people with high salt intake have unhealthy lifestyles, and that there is a higher risk of obese than people without high salt intake (43, 44). However, this study did not fully consider lifestyle. Therefore, there might be unknown confounders. Fifth, the impact of each antidiabetic or antihypertensive medication on sodium excretion is different (45–51). However, this study did not fully consider the impact of antidiabetic or antihypertensive medications on sodium excretion. Moreover, NAFLD itself may affect sodium excretion by affecting the renin-angiotensin system (52). Finally, diagnosis of NAFLD was not performed using liver biopsy, although it is the gold standard. Moreover, we did not use other non-invasive techniques, such as ultrasound, FibroScan, or MRI, for the diagnosis of fatty liver (53). However, the correlation between HSI and the definition of NAFLD using ultrasonography has been assessed (30).

In conclusion, to the best of our knowledge, the present study shows that salt intake is related to the prevalence of NAFLD in patients with T2D. It is suggested that the control of salt intake is crucial not only for blood pressure and CVD prevention but also for the prevention of NAFLD in patients with T2D.

**DATA AVAILABILITY STATEMENT**

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.
ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Kyoto Prefectural University of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FT designed the work, analyzed and interpreted the data, and wrote the manuscript. YH conceived and designed the work, acquired, analyzed, interpreted the data, and revised the manuscript. AK and RS conceived and designed the study, acquired data, and contributed to the discussion.

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