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ORIGINAL RESEARCH

Associations of Dietary Salt and Its Sources with Hemoglobin A1c in Patients with Type 2 Diabetes Not Taking Anti-Diabetic Medications: Analysis Based on 6-Month Intervention with a Moderate Low-Carbohydrate Diet

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Objective: Based on biological studies, the hyperglycemic effect mediated by sodium-glucose co-transporter 1 in the intestine is stronger for foods containing more sodium chloride. Observational studies have demonstrated that type 2 diabetes (T2DM) incidence increases as salt intake increases. We aimed to elucidate associations of total salt and its sources with hemoglobin A1c (HbA1c) in patients with T2DM.

Methods: We conducted an observational study using data from a 6-month moderate low-carbohydrate dietary intervention in 245 outpatients with T2DM (138 men) without antidiabetic medication. Intakes of total salt and its sources, carbohydrate and total energy were assessed at baseline and 6 months based on 3-day dietary records. Multiple regression analyses were performed to examine associations of Δtotal salt or its sources with ΔHbA1c.

Results: Salt intake significantly decreased in men (change: −0.92 ± 3.53 g/day) but not in women (0.11 ± 2.28). HbA1c (men: −1.5 ± 1.6%; women: −0.9 ± 1.3%), carbohydrate (men: −115 ± 104 g/day; women: −64 ± 71) and total energy (men: −439 ± 660 kcal/day; women: −192 ± 438) significantly decreased in both sexes. Multiple regression analysis revealed that reducing intakes of total salt and salt from salty snacks, meat processed foods, Chinese noodles with soup and table salt by 1.0 g was associated with decreases in HbA1c of 0.11% 1.18% 0.47% 0.38% and 0.26%, respectively, in men, while reducing salt from miso by 1.0 g was associated with a decrease in HbA1c of 0.30% in women. The associations were dependent on Δcarbohydrate or Δtotal energy in men, while the association of Δsalt from miso in women was independent of them.

Conclusion: Reducing total salt and its sources had differential associations with HbA1c. Individual associations depended on Δcarbohydrate or Δtotal energy in men, while that of salt from miso in women was independent of them.

Keywords: salt intake, dietary sodium, salt sources, carbohydrate intake, hemoglobin A1c, low-carbohydrate diet

Introduction

People in East Asian countries consume more salt (10–12 g/day) than their Western counterparts (7 g/day).[1,2] This greater salt intake is the leading dietary risk for higher blood pressure, a risk factor for cardiovascular diseases in East Asian countries, predominantly stroke.[3,4] Observational studies have proven that greater salt intake increases incidences of type 2 diabetes (T2DM)[5,6] and complications as

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well as mortality,[7–9] but reasons are unknown. Human and animal studies have suggested that salt intake worsens insulin resistance, but the relationship between it and insulin resistance is still controversial.[8,10] Regarding salt intake and T2DM, a dietary survey on a civilian East Asian population demonstrated that urinary sodium excretion increased in pace with an increase in carbohydrate intake.[11] Increased salt intake is closely associated with increased intake of carbohydrate, the macronutrient with the strongest hyperglycemic effects,[12] but this was ignored by past observational studies or reviews.[8,13,14]

In terms of cell biology, glucose absorption taking place in small intestinal cells is mediated by the sodium-glucose co-transporter 1 (SGLT1), which is driven by sodium extrusion.[15] It is theoretically possible that foods containing more sodium chloride have a stronger hyperglycemic effect.

Our previous interventional study with a moderate low-carbohydrate diet in patients with T2DM revealed that reducing carbohydrate intake from Chinese soup noodles (7 g salt) by 50 g was associated with a decrease in hemoglobin A1c (HbA1c) of 0.82%, which was 2.5-fold greater than that for the same reduction in carbohydrate intake from rice (0 g salt).[16] Single servings of Chinese soup noodles have a higher sodium chloride concentration than rice.

In consideration of the above, we hypothesized that salt intake itself might have hyperglycemic effects in the clinical setting. However, quantitative information on the direct impact of intake of salt and its sources on HbA1c in patients with T2DM has not been reported.

HbA1c indicates the mean level of an individual's long-term glucose exposure and is the gold standard for long-term glycemic control. Although HbA1c is a function of both fasting plasma glucose (FPG) and postprandial glucose (PPG), it has been reported that the contributions of FPG and PPG to HbA1c differ according to HbA1c levels. The relative contribution of PPG is predominant in fairly controlled patients with T2DM, whereas the contribution of FPG increases gradually as their disease worsens.[17,18]

We, therefore, investigated associations of changes in intake of salt and its sources with those in HbA1c based on data from patients with T2DM who followed a moderate low-carbohydrate diet over 6 months in our previous study.[16] Concomitant changes in carbohydrate and total energy intake were also considered. We additionally evaluated associations of changes in salt and its sources with those in FPG. Patients taking any type of anti-diabetic medication, which would lead to an incorrect estimate of changes in HbA1c, were excluded.

Methods

Patients

We recruited all new Japanese outpatients with T2DM and HbA1c levels of 6.5% or above at Haimoto Clinic from March 2013 to June 2018. Inclusion criteria included: patient aged from 20 to 80 years who met the National Diabetes Data Group criteria for T2DM,[19] newly or previously diagnosed patient, patient who agreed to dietary therapy with a moderate low-carbohydrate for 6 months without anti-diabetic medication. Exclusion criteria included: taking any type of oral hypoglycemic agent, insulin or steroid hormone from 3 months before baseline that would impact HbA1c levels; following strict carbohydrate restriction at baseline based on commercial diet therapies such as the Atkins diet; serum creatinine levels greater than 2.0 mg/dl (176.8 μmol/l), ketoacidosis, soft drink ketosis, cancer or decompensated liver cirrhosis.

Of 159 eligible Japanese male outpatients, 2 declined to participate, 9 were voluntarily lost to follow-up, 1 moved, 4 did not report dietary information, and 3 suffered from cancer and 2 took anti-diabetic medications during the study period. Thus, 138 male patients were investigated. Of 117 eligible Japanese female outpatients, 3 declined to participate, 5 were voluntarily lost to follow-up, 1 suffered from cancer and 1 took anti-diabetic medications during the study period. Thus, 107 female patients were investigated. The average age of patients remaining for the analysis was 60.0 ± 11.0 years in men (range: 26–78) and 61.8 ± 10.4 years in women (range: 34–80). Among them, 46% of the male and 45% of the female patients took anti-hypertensive medications, and 22% of the male and 36% of the female patients took lipid-lowering medications.

After obtaining written informed consent, patients were followed up for 6 months. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Aichi Shukutoku University (Approval number: 2020–3). It was registered in University Hospital Medical Network (UMIN000009866) before its start.

Sources of Salt from Various Foods

Salt-rich foods were divided into 11 groups: soy sauce, table salt, miso (soybean paste fermented long-term with salt), Chinese noodles, Chinese noodles with soup, udon

(thick white wheat noodles), bread, fish and roe processed foods, meat processed foods, salty snacks and pickled vegetables, according to the Japanese food composition table Data were shown as salt equivalent [1g salt (sodium chloride) = sodium (mg) × 2.54/1000].

Moderate Low-Carbohydrate Diet, Dietary Records and HbA1c

The main principles of our moderate low-carbohydrate diet are as follows: first, to calculate carbohydrate intake from 3-day dietary records at baseline; second, to reduce carbohydrate intake according to patients' baseline HbA1c levels.[20] Based on the results of our previous studies,[16,20–22] patients were divided into 3 groups according to their baseline HbA1c: ≤ 7.4%, 7.5–8.9% and ≥ 9.0%. Patients with HbA1c levels ≤ 7.4% were instructed to reduce carbohydrate intake by about 70 g, those with levels 7.5–8.9% were instructed to reduce carbohydrate intake by about 120 g and those with levels ≥ 9.0% to reduce carbohydrate intake by about 170 g. Patients were recommended to eat an amount of fat corresponding to the decrease in energy due to the reduced carbohydrate intake. A dietician (SW, Shio Watanabe) gave instructions to all participants twice during the first month and once a month thereafter.

We left salt intake up to patients, not instructing them to reduce or increase intake of salt and its sources.

The target HbA1c levels were based on the guidelines of the American Diabetes Association.[19] Patients were requested to maintain their usual level of physical activity throughout the study.

Dietary Records and Clinical Assessment

Intakes of total salt and its sources, carbohydrate and other macronutrients were assessed at baseline and 6 months based on 3-day dietary records. Patients were requested to record dietary intakes on 3 non-consecutive days: 2 weekdays and a holiday. Additional information was obtained in an interview with a dietitian. Dietary intakes were computed from the dietary records using the Healthy Maker Pro 501 software (Mushroomsoft, Okayama, Japan). Intakes of nutrients and energy were estimated using the Standard Tables of Food Composition in Japan (8th edition, 2020).

Blood pressure was measured by nurses using an upper arm cuff oscillometric blood pressure device (HBP-9020; Omron, Kyoto, Japan), in a sitting position after 3 min of rest. Body weight was determined using an electronic scale while patients were wearing only underwear. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. We measured the BMI, blood pressure and HbA1c level of each patient every month. Venous blood samples were obtained after an overnight (12-h) fast at baseline and 6 months for the determination of fasting plasma glucose (FPG), fasting serum insulin, triglycerides, LDL (low-density lipoprotein)-cholesterol and HDL (high-density lipoprotein)-cholesterol.

Laboratory Methods

HbA1c levels were measured by high-performance liquid chromatography (Arkley Co., Kyoto, Japan) and presented as National Glycohemoglobin Standardization Program (NGSP) values (%). Fasting plasma glucose concentrations were determined using enzymatic methods (Shino-Test Co., Kanagawa, Japan). Fasting serum insulin levels were measured using the standard double antibody radioimmunoassay method (Fujirebio Inc., Tokyo, Japan). Enzymatic methods were used to measure serum triglyceride concentrations (Daiichi Pure Chemicals Co., Tokyo, Japan). Direct methods were used to assay serum LDL-cholesterol and HDL-cholesterol levels (Daiichi Pure Chemicals Co., Tokyo, Japan).

Statistical Analysis

Changes in HbA1c, BMI, cardiovascular risk factors, total salt and its sources, total carbohydrate and other macronutrients (Δ) were defined as the level after 6 months minus the baseline level. To evaluate the changes, the Wilcoxon test or its parametric version (paired *t*-test) was used, depending on their distributions.

We also conducted stratified analysis by tertile of reduction in carbohydrate intake (ΔC1-C3-patients) to evaluate more detailed associations of changes in total salt intake with those of HbA1c, considering changes in carbohydrate or energy intake.

Multiple regression analyses with adjustment for age plus ΔBMI (Model 1) or age, ΔBMI plus Δtotal carbohydrate (Model 2) or age, ΔBMI plus Δtotal energy (Model 3) were performed to examine associations of Δtotal salt or Δsalt from sources with ΔHbA1c. We additionally conducted the Model 1–3 analyses to examine associations of Δtotal salt or Δsalt from sources with ΔFPG.

P values less than 0.05 were considered statistically significant. Data are shown as mean ± SD. All statistical analyses were performed using SPSS (version 25.0).

Results

Changes in HbA1c and Other Cardiovascular Risk Factors During 6 Months in Both Sexes

Compared to baseline, the mean HbA1c levels significantly decreased over 6 months in both sexes, by 1.5 ± 1.6% from 8.3 ± 1.7% at baseline in men, and by 0.9 ± 1.3% from 7.8 ± 1.5% at baseline in women (Table 1).

The mean systolic and diastolic blood pressure also significantly decreased in both sexes. The mean BMI, plasma glucose levels, fasting insulin levels, serum LDL-cholesterol, HDL-cholesterol and triglyceride levels significantly improved in both sexes (Table 1).

Changes in Intakes of Total Salt and Its Sources, Carbohydrate, Total Energy and Other Macronutrients During 6 Months in Men

The mean total salt and carbohydrate intakes significantly decreased over 6 months, by 0.92 ± 3.53 g/day, from 10.58 ± 3.08 g/day at baseline and by 115 ± 104 g/day, from 285 ± 94 g/day at baseline, respectively (Table 2). The mean total energy intake significantly decreased, by 439 ± 660 kcal/day, from 2285 ± 753 kcal/day at baseline, whereas mean fat intake significantly increased and changes in protein intake were not significant.

As for salt sources, salt intake from Chinese noodles with or without soup, bread and salty snacks significantly decreased, while salt intake from meat processed foods significantly increased (Table 2).

Multiple regression analysis revealed that total salt intake decreased in pace with reductions in carbohydrate intake and reducing total carbohydrate intake by 10.0 g was associated with a decrease in total salt intake of 0.13 g ($\beta = 0.13$, SE = 0.03, $P < 0.001$ adjusted for age).

Changes in Intakes of Total Salt and Its Sources, Carbohydrate, Energy and Other Macronutrients During 6 Months in Women

Over 6 months, the mean change in total salt intake, from 8.93 ± 1.99 to 9.03 ± 2.05 g/day, was not significant, whereas mean total carbohydrate intake significantly decreased, by 64 ± 71 g/day, from 230 ± 67 to 166 ± 43 g/day (Table 2).

The mean total energy intake significantly decreased, by 192 ± 438 kcal/day, from 1745 ± 431 kcal/day, and fat intake significantly increased, but changes in protein intake were not significant (Table 2). These results were similar to those for men. Regarding salt sources, salt from bread and salty snacks significantly decreased (Table 2).

Table 1 Hemoglobin A1c and Cardiovascular Risk Factors at Baseline and Their Changes During 6 Months by Sex

	Men (n = 138)				Women (n = 107)			
	Baseline	**6 Months**	**Changes**	***P***	**Baseline**	**6 Months**	**Changes**	***P***
Age	60.0 ± 11.0				61.8 ± 10.4			
Duration of diabetes (month)	26.9 ± 52.8				23.2 ± 51.3			
Body mass index (kg/m^2)	25.5 ± 3.5	24.7 ± 3.4	−0.8 ± 1.2	< 0.001	25.1 ± 4.1	24.3 ± 4.0	−0.8 ± 1.3	< 0.001
Hemoglobin A1c (%)	8.3 ± 1.7	6.7 ± 0.7	−1.5 ± 1.6	< 0.001	7.8 ± 1.5	6.9 ± 0.7	−0.9 ± 1.3	< 0.001
Hemoglobin A1c (mmol/mol)	66.7 ± 18.3	50.0 ± 8.0	−16.7 ± 17.2	< 0.001	61.8 ± 16.9	51.6 ± 7.6	−10.2 ± 14.0	< 0.001
Plasma glucose levels (mmol/l)	8.16 ± 2.05	6.99 ± 1.28	−1.17 ± 1.72	< 0.001	7.66 ± 2.44	6.77 ± 1.39	−0.94 ± 1.72	< 0.001
Fasting insulin levels (pmol/l)	52.4 ± 32.4	45.7 ± 31.2	−6.7 ± 23.5	< 0.001	58.4 ± 42.3	53.3 ± 43.7	−5.1 ± 29.0	0.014
LDL-cholesterol (mmol/l)	3.42 ± 0.91	3.24 ± 0.78	−0.18 ± 0.96	0.030*	3.47 ± 0.80	3.18 ± 0.75	−0.28 ± 0.85	0.001
HDL-cholesterol (mmol/l)	1.30 ± 0.28	1.42 ± 0.31	0.13 ± 0.23	< 0.001	1.53 ± 0.39	1.63 ± 0.36	0.10 ± 0.23	< 0.001
Triglycerides (mmol/l)	1.83 ± 2.44	1.39 ± 1.06	−0.44 ± 1.89	< 0.001	1.49 ± 0.91	1.26 ± 0.76	−0.23 ± 0.63	0.001
Systolic blood pressure (mmHg)	140 ± 20	132 ± 13	−8 ± 18	< 0.001	138 ± 17	127 ± 10	−10 ± 17	< 0.001
Diastolic blood pressure (mmHg)	84 ± 13	81 ± 11	−3 ± 14	0.001	79 ± 11	74 ± 8	−5 ± 11	< 0.001*
Anti-hypertensive medications		46%				45%		
Lipid-lowering medications		22%				36%		

Notes: Change was defined as the level after 6 months minus the level at baseline. *Paired *t*-test was used, and Wilcoxon test was used for the others.
Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 2 Changes in Macronutrients, Total Salt and Its Sources at Baseline and Their Changes During 6 Months by Sex

	Men (n=138)				Women (n=107)			
	Baseline	**6 Months**	**Changes**	***P***	**Baseline**	**6 Months**	**Changes**	***P***
Total energy (kcal)	2285 ± 753	1846 ± 521	−439 ± 660	< 0.001	1745 ± 431	1553 ± 342	−192 ± 438	< 0.001
Carbohydrate (g/day)	285 ± 94	170 ± 58	−115 ± 104	< 0.001	230 ± 67	166 ± 43	−64 ± 71	< 0.001
% Carbohydrate	50.8 ± 9.7	37.8 ± 11.5	−13.0 ± 11.3	< 0.001	52.6 ± 7.7	43.5 ± 9.3	−9.1 ± 9.7	< 0.001
Protein (g/day)	80 ± 24	82 ± 28	2 ± 26	0.797	68 ± 15	70 ± 18	3 ± 19	0.180
% Protein	14.2 ± 2.4	17.7 ± 3.3	3.5 ± 3.7	< 0.001	15.8 ± 2.5	18.2 ± 2.9	2.4 ± 3.3	< 0.001
Fat (g/day)	70 ± 30	76 ± 32	6 ± 33	<0.001	58 ± 21	64 ± 23	6 ± 23	0.022
% Fat	27.3 ± 7.0	36.5 ± 9.6	9.2 ± 10.4	< 0.001	29.8 ± 6.9	36.2 ± 8.0	6.5 ± 8.5	< 0.001
Total salt intake (g/day)	10.58 ± 3.08	9.65 ± 2.83	−0.92 ± 3.53	0.003*	8.93 ± 1.99	9.03 ± 2.05	0.10 ± 2.28	0.635*
Salt by source (g/day)								
Soy sauce	2.53 ± 1.21	2.35 ± 1.20	−0.19 ± 1.51	0.228	2.06 ± 1.03	2.21 ± 1.05	0.14 ± 1.38	0.232
Table salt	1.85 ± 0.94	1.78 ± 0.97	−0.08 ±1 .20	0.552	1.59 ± 0.77	1.56 ± 0.77	−0.03 ± 0.91	0.378
Miso	1.03 ± 0.83	0.90 ± 0.73	−0.14 ± 0.98	0.246	0.99 ± 0.82	1.07 ± 0.86	0.09 ± 0.99	0.097
Chinese noodles	0.53 ± 1.05	0.23 ± 0.49	−0.30 ± 1.11	0.003	0.24 ± 0.67	0.14 ± 0.35	−0.10 ± 0.77	0.625
Chinese noodles with soup	1.17 ± 1.78	0.65 ± 1.08	−0.53 ± 1.91	0.006	0.51 ± 1.04	0.29 ± 0.65	−0.22 ± 1.27	0.188
Udon	0.32 ± 0.84	0.17 ± 0.43	−0.14 ± 0.81	0.109	0.13 ± 0.28	0.19 ± 0.45	0.06 ± 0.52	0.646
Bread	0.63 ± 0.54	0.51 ± 0.50	−0.12 ± 0.53	0.005	0.68 ± 0.53	0.57 ± 0.46	−0.11 ± 0.59	0.035
Fish and roe processed foods	0.75 ± 0.66	0.74 ± 0.73	0.00 ± 1.00	0.579	0.55 ± 0.50	0.69 ± 0.59	0.14 ± 0.78	0.053
Meat processed foods	0.52 ± 0.48	0.68 ± 0.59	0.17 ± 0.61	0.002	0.37 ± 0.41	0.43 ± 0.41	0.06 ± 0.52	0.152
Salty snacks	0.10 ± 0.22	0.03 ± 0.08	−0.06 ± 0.22	0.004	0.12 ± 0.24	0.04 ± 0.09	−0.08 ± 0.25	0.001
Pickled vegetables	0.38 ± 0.50	0.44 ± 0.64	0.06 ± 0.75	0.893	0.27 ± 0.44	0.32 ± 0.45	0.05 ± 0.56	0.362

Notes: Change was defined as the level after 6 months minus the level at baseline. *Paired *t*-test was used, and Wilcoxon test was used for the others.

Total salt intake decreased in pace with reductions in carbohydrate intake and reducing total carbohydrate intake by 10.0 g was associated with a decrease in total salt intake of 0.13 g (β = 0.13, SE = 0.03, $P < 0.001$ adjusted for age).

Associations of Changes in Total Salt Intake with Changes in HbA1c (%) in All Patients and Patients by Tertile of Reductions in Carbohydrate Intake by Sex

In men, Model 1 multiple regression analysis indicated a positive, significant correlation with ΔHbA1c for Δtotal salt intake and reducing total salt by 1.0 g was correlated with a HbA1c decrease of 0.11% in all patients. With the adjustment in Model 2 or Model 3, the significant correlation disappeared (Table 3).

Total carbohydrate intake significantly changed from baseline, by −16 ± 42 g/day in ΔC1-patients (n = 46, $P = 0.007$), −106 ± 19 g/day in ΔC2-patients (n = 46, $P < 0.001$) and −224 ± 91 g/day in ΔC3-patients (n = 46, $P < 0.001$). The change in total salt intake was greatest and significantly different in ΔC3-patients (−2.31 ± 4.09 g/day, $P = 0.001$), but not in ΔC1 (−0.21 ± 2.50 g/day, $P = 0.369$) or ΔC2-patients (−0.23 ± 3.50 g/day, $P = 0.394$). The stratified analysis according to Model 1 indicated a positive, significant correlation of Δtotal salt intake with ΔHbA1c in ΔC3-patients, but not in ΔC1 or ΔC2-patients. With the adjustment in Model 2 or Model 3, the significant correlation disappeared (Table 3).

In women, Model 1, Model 2 or Model 3 multiple regression analysis indicated no significant correlation of Δtotal salt intake with ΔHbA1c in all patients (Table 3). Total carbohydrate intake changed from baseline, not significantly by −5 ± 25 g/day in ΔC1-patients (n = 36, $P = 0.694$), and significantly by −56 ± 16 g/day in ΔC2-patients (n = 36, $P < 0.001$) and −142 ± 59 g/day in ΔC3-patients (n=35, $P < 0.001$). Reductions in total salt intake were significant in ΔC3-patients (−0.99 ± 1.89 g/day, $P = 0.005$), but not in ΔC1 (1.32 ± 2.13 g/day, $P = 0.001$) or ΔC2-patients (−0.04 ± 2.22 g/day, $P = 0.915$). The stratified analysis according to Model 1, Model 2 or Model 3 indicated no significant correlation of Δtotal salt intake with ΔHbA1c in ΔC1, ΔC2 or ΔC3-patients (Table 3).

Associations of Changes in Salt from Sources with Changes in HbA1c (%) in Men

Model 1 analysis indicated positive, significant correlations with ΔHbA1c for Δsalt from salty snacks, meat processed

Table 3 Associations of Changes in Total Salt Intake with Changes in Hemoglobin A1c (%) in All Patients and Patients by Tertile of Reductions in Carbohydrate Intake by Sex

	Regression Model								
	Model 1			Model 2			Model 3		
	β	SE	*P*	β	SE	*P*	β	SE	*P*
Men									
All patients (n = 138)	0.107	0.035	0.003	0.024	0.033	0.466	0.025	0.039	0.520
ΔC1-patients (n = 46)	0.019	0.032	0.561	0.019	0.033	0.566	0.023	0.033	0.490
ΔC2-patients (n = 46)	−0.052	0.052	0.326	−0.045	0.052	0.401	−0.035	0.058	0.549
ΔC3-patients (n = 46)	0.168	0.023	0.010	0.102	0.072	0.162	0.130	0.079	0.107
Women									
All patients (n = 107)	0.070	0.051	0.176	−0.032	0.049	0.524	−0.019	0.056	0.734
ΔC1-patients (n = 36)	−0.003	0.030	0.912	−0.026	0.032	0.423	−0.008	0.036	0.815
ΔC2-patients (n = 36)	−0.072	0.075	0.344	−0.077	0.075	0.314	−0.075	0.078	0.343
ΔC3-patients (n = 35)	0.047	0.028	0.109	0.039	0.145	0.204	1.96×10^{-4}	0.150	1.000

Notes: Model 1: adjusted for age plus Δbody mass index (BMI). Model 2: adjusted for age, ΔBMI plus Δcarbohydrate (g/day). Model 3: adjusted for age, ΔBMI plus Δtotal energy (kcal). ΔC1 - 3 patients: Patients were stratified by tertile of reductions in carbohydrate intake. In men, reduction in carbohydrate intake was greatest in ΔC3-patients (224 ± 91 g/day) followed by ΔC2-patients (106 ± 19 g/day) and ΔC1-patients (16 ± 42 g/day) in descending order. In women, reduction in carbohydrate intake was greatest in ΔC3-patients (142 ± 59 g/day) followed by ΔC2-patients (56 ± 16 g/day) and ΔC1-patients (5 ± 25 g/day) in descending order.
Abbreviation: SE, standard error.

foods, Chinese noodles with or without soup and table salt (Table 4). Reducing them by 1.0 g was correlated with HbA1c decreases of 1.18%, 0.47%, 0.23%, 0.38% and 0.26%, respectively. This analysis also indicated an inverse, significant correlation with ΔHbA1c for Δsalt from udon. With the adjustment in Model 2, the significant correlations disappeared for Δsalt from all sources (Table 4). With the adjustment in Model 3, most significant correlations disappeared, but a significant correlation remained for Δsalt from Chinese noodles with or without soup.

Associations of Changes in Salt from Sources with Changes in HbA1c (%) in Women

The only positive correlation of ΔHbA1c was with Δsalt from miso in Model 1 analysis (Table 5), and reducing salt

Table 4 Associations of Changes in Salt from Sources with Changes in Hemoglobin A1c (%) in Men (n = 138)

Salt by Sources	Regression Model								
	Model 1			Model 2			Model 3		
	β	SE	*P*	β	SE	*P*	β	SE	*P*
ΔSoy sauce	0.063	0.086	0.466	−0.036	0.073	0.624	−0.065	0.083	0.432
ΔTable salt	0.258	0.105	0.016	0.062	0.094	0.516	0.103	0.105	0.330
ΔMiso	−0.094	0.135	0.481	−0.024	0.112	0.931	−0.148	0.123	0.231
ΔChinese noodles	0.383	0.117	0.001	0.155	0.107	0.148	0.246	0.115	0.034
ΔChinese noodles with soup	0.229	0.067	0.001	0.099	0.061	0.109	0.144	0.066	0.032
ΔBread	0.419	0.238	0.080	−0.001	0.210	0.996	0.196	0.226	0.386
ΔUdon	−0.347	0.154	0.026	−0.215	0.131	0.104	−0.273	0.143	0.059
ΔFish and roe processed foods	0.031	0.129	0.808	0.044	0.108	0.684	−0.031	0.119	0.797
ΔMeat processed foods	0.470	0.205	0.024	0.291	0.175	0.100	0.159	0.205	0.439
ΔSalty snacks	1.177	0.569	0.040	0.819	0.482	0.091	0.987	0.527	0.063
ΔPickled vegetables	0.137	0.173	0.429	0.064	0.146	0.661	0.134	0.159	0.403

Notes: The change in hemoglobin A1c and total salt and its sources (Δ) was defined as the level after 6 months minus the level at baseline. Model 1: adjusted for age plus Δbody mass index (BMI). Model 2: adjusted for age, ΔBMI plus Δcarbohydrate (g/day). Model 3: adjusted for age, ΔBMI plus Δtotal energy (kcal).
Abbreviation: SE, standard error.

Table 5 Associations of Changes in Salt from Sources with Changes in Hemoglobin A1c (%) in Women (n = 107)

Salt by Sources	Regression Model								
	Model 1			Model 2			Model 3		
	β	SE	*P*	β	SE	*P*	β	SE	*P*
ΔSoy sauce	0.010	0.085	0.908	−0.703	0.076	0.343	−0.046	0.082	0.573
ΔTable salt	−0.057	0.129	0.662	−0.041	0.114	0.722	−0.142	0.123	0.252
ΔMiso	0.303	0.116	0.010	0.230	0.104	0.029	0.257	0.111	0.023
ΔChinese noodles	−0.002	0.157	0.991	−0.104	0.139	0.459	0.020	0.149	0.891
ΔChinese noodles with soup	−0.054	0.096	0.576	−0.086	0.084	0.307	−0.041	0.091	0.655
ΔBread	0.291	0.197	0.144	0.191	0.176	0.280	0.215	0.188	0.257
ΔUdon	0.238	0.225	0.294	−0.103	0.209	0.822	0.090	0.218	0.680
ΔFish and roe processed foods	−0.081	0.153	0.596	−0.096	0.134	0.479	−0.181	0.146	0.217
ΔMeat processed foods	−0.052	0.227	0.820	−0.182	0.200	0.366	−0.312	0.222	0.163
ΔSalty snacks	0.918	0.473	0.055	0.161	0.449	0.722	0.747	0.452	0.101
ΔPickled vegetables	0.107	0.208	0.608	0.209	0.184	0.257	0.228	0.198	0.254

Notes: The change in hemoglobin A1c and total salt and its sources (Δ) was defined as the level after 6 months minus the level at baselineModel 1: adjusted for age plus Δbody mass index (BMI). Model 2: adjusted for age, ΔBMI plus Δcarbohydrate (g/day). Model 3: adjusted for age, ΔBMI plus Δtotal energy (kcal).
Abbreviation: SE, standard error.

from miso by 1.0 g was correlated with a decrease in HbA1c of 0.30%. The significant correlation of Δsalt from miso remained in Model 2 and Model 3.

Associations of Changes in Total Salt and Its Sources with Changes in Fasting Plasma Glucose in Both Sexes

Additional multiple regression analysis was performed to assess associations of Δtotal salt and its sources with ΔFPG (mmol/l).

In men, Model 1 analysis indicated no significant association for Δtotal salt or Δsalt from sources. Model 2 and 3 analyses produced the same results. In women, Model 1 analysis indicated no significant association for Δtotal salt, but positive and significant associations for Δsalt from salty snacks (β = 1.94, SE = 0.63, P = 0.003) and Δsalt from miso (β = 0.38, SE = 0.16, P = 0.018). With the adjustment in Model 2 or 3, the significant correlation disappeared for Δsalt from salty snacks, but the significant correlation of Δsalt from miso remained.

Discussion

The current study showed that: (1) Total salt intake significantly decreased in male but not in female patient; (2) Reducing total salt by 1.0 g was associated with a decrease in HbA1c of 0.11% in men; (3) Reducing salt from individual sources by 1.0 g had differential associations with HbA1c; (4) The associations with ΔHbA1c were dependent on Δcarbohydrate or Δtotal energy intake in men, but independent of them for Δsalt from miso in women.

The biological plausibility of foods containing more sodium chloride having a stronger hyperglycemic effect mediated by SGTL-1 in the intestine[15] was not proven in this study. This is explained in the following.

First, there was only a positive correlation in male ΔC3-patients, whose reductions in total salt and carbohydrate were greatest. Statistically, there was more inter-individual variation in Δcarbohydrate and greater reductions in total salt were associated with greater reductions in carbohydrate, resulting in a stronger correlation of reduction in total salt with decrease in HbA1c. In contrast, since the effects of Δcarbohydrate were limited in ΔC1 and ΔC2-patients due to smaller inter-individual variation, associations of Δtotal salt with ΔHbA1c were minimal. Second, the positive correlation of Δtotal salt or Δsalt from sources disappeared with adjustment for Δcarbohydrate. Third, the regression coefficient was smaller for Chinese noodles with soup (containing 7 g salt) than Chinese noodles without soup (containing 3 g salt) although the two sources included the same amount of carbohydrate and the salt content of the former was 2-fold higher than that of the latter.

There were reductions in total energy intake of 10–20% during the study period. The reduction in total energy was due to reduction in carbohydrate intakes because only these intakes decreased; mean fat intakes increased and mean protein intakes did not change

during the study period in both sexes. This is the reason why the Model 2 and Model 3 analyses produced the same results for the association of Δtotal salt and Δsalt from 4 sources (table salt, udon, meat processed foods and salty snacks) in men. Moreover, the associations of Δsalt from Chinese noodles with or without soup were also dependent on Δtotal carbohydrate intake and independent of Δtotal energy intake in men. Thus, the above suggests that Δtotal carbohydrate intake has a dominant effect on ΔHbA1c over Δtotal energy intake for Δsalt from these 6 sources. On the other hand, the results for Δsalt from miso in women were somewhat conflicting. The association was independent of either Δtotal carbohydrate or Δtotal energy. On the basis of the purpose, design and results of this study, it is difficult to resolve whether carbohydrate or energy plays the dominant role in the effect on HbA1c, but even so, the result for salt from miso in women was unique among the salt sources.

There were sex differences in the association of reductions in total salt intake with decreases in HbA1c. According to the results of a recent health survey in Japan,[23] men consume more carbohydrate and salt than women, which was also found in the present study. As we noted in our previous paper,[16] higher carbohydrate and salt intakes at baseline would result in larger decreases in carbohydrate and salt, which could lead to bigger changes in HbA1c. Compared with male patients, female patients had lower total salt and carbohydrate intakes and exhibited lower HbA1c levels at baseline. Also, a lack of change in total salt intake was accompanied by lower reductions in carbohydrate intake and HbA1c changed less during the study period. This explains why Δtotal salt was not correlated with ΔHbA1c in female patients. We should pay attention to male ΔC3-patients, men with a mean age of 54 years and the highest salt and carbohydrate intakes and HbA1c.

Among our results, that for salt from miso in women was unexpected and of greater interest than those for other salt sources. Miso (soybean paste fermented long-term with salt) is a salty condiment and ranked third for salt consumption in this study. Reducing salt from miso by 1.0 g was correlated with a decrease in HbA1c of 0.30% in female patients and, notably, the association was independent of reductions in total carbohydrate or total energy. The association was not found in men. These results suggest that consumption of miso has detrimental effects on glucose metabolism in women, which seems inconsistent with previous studies finding that soy-based food and its components prevent the development of T2DM[24,25] and is associated with reduced insulin resistance in Japanese populations.[26,27] In addition, soy products are rich sources of isoflavones that structurally resemble estrogen. Estrogen has beneficial effects on glucose homeostasis and prevention of diabetes, and several trials have suggested that menopausal hormone therapy reduces the incidence of T2DM in women.[28] The average age of our female patients was 61.8 ± 10.4 years old, and most of them were postmenopausal. On the other hand, dietary soy isoflavones have been reported to inhibit the effects of estrogen in the postmenopausal breast.[29] Thus, it is also possible that isoflavones have adverse effects on glucose metabolism in postmenopausal women and in this regard, a cohort study reported that soy intake was positively associated with the risk of diabetes.[30] In any case, further studies are required to clarify the effects of a soy product like miso on glucose metabolism.

Our findings for salt from salty snacks and udon in men were also highly interesting, so we should address them in the future. Reducing salt intake from salty snacks by 1.0 g was associated with a decrease in HbA1c of 1.18% in men, which was the greatest among salt sources. This was in spite of the fact that the reduction of salt from salty snacks was the smallest among salt sources. Having the greatest decreases in HbA1c would be reasonable and is explained by the following: single servings of popular Japanese salty snacks contain quite small amounts of salt (about 1.0 g) but have higher carbohydrate contents (about 30–75g). Our previous study revealed that reducing carbohydrate from snacks by 50 g was associated with a decrease in HbA1c of 0.88%.[16] Reducing salt from udon by 1.0 g was associated with an increase in HbA1c of 0.35%, in contrast to other salt sources, in men. One possible explanation for this inverse association is instability in the regression model due to the small percentage of patients who consumed udon (33%). Another possible explanation is that patients who decreased salt by consuming less udon did not reduce other carbohydrate sources so much. Actually, patients who decreased salt from udon had significantly lower reductions ($P = 0.043$) in carbohydrate from rice (−42.1 ± 67.9 g/day) compared to patients who did not change or increased the amount of salt from udon (−67.1 ± 60.3 g/day).

In the current study, while Δtotal salt intake was significantly associated with ΔHbA1c, there was no association between Δtotal salt intake and ΔFPG. As we mentioned earlier in the Introduction section, the contributions of FPG and PPG to HbA1c differ according to HbA1c levels. The relative contribution of PPG is

predominant in fairly controlled patients with HbA1c levels less than 7.3%, whereas FPG plays the major role at HbA1c levels above 8.4%.[17] Since average patient HbA1c levels were 8.3% in men and 7.8% in women in the current study, ΔFPG had less impact on ΔHbA1c than ΔPPG. This suggests that the significant associations of Δtotal salt intake with ΔHbA1c were mediated by changes in PPG.

Patients greatly and significantly reduced carbohydrate intake and significantly increased fat intake by following a moderate low-carbohydrate diet. Meta-analyses of many studies have revealed that carbohydrate restriction reduces serum triglycerides and increases HDL-cholesterol despite a corresponding increase in fat intake, but changes in LDL-cholesterol are controversial.[31] Actually, the current study, and our previous studies[16,21,22,32] produced almost the same results. Regarding an association of Δsalt intake with Δserum lipid profiles, we found no association for Δtriglyceride, ΔHDL-cholesterol or ΔLDL-cholesterol levels (data not shown), suggesting that salt intake does not affect serum lipid profiles.

The first strength of our study is elimination of patients taking any type of anti-diabetic medication, which would lead to incorrect estimates of HbA1c changes. Another strength is that 3-day dietary records enabled us to evaluate intakes of total salt and its sources and total carbohydrate.

As limitations, first, this study was not designed to directly reduce salt intake but was an observational study based on our previous interventional study regarding effects of reductions in carbohydrate sources on decreases in HbA1c. Actually, there was a small reduction in total salt intake of 0.90 g in men and no change in women. However, focusing on individual salt sources, salt from several of them was significantly reduced in both sexes and reducing them had differential associations with HbA1c. We therefore believe that our purpose was substantially achieved within the limited design of the study, particularly with regard to patients in East Asian countries who consume a lot of salt. Second, the regression model would have been unstable due to the small percentages of patients who consumed udon (33%) and salty snacks (29%) in men and Chinese soup noodles (30%) and udon (35%) in women. Third, there were no correlations in patients with lower salt and carbohydrate consumption at baseline and smaller changes in these nutrients, making our results less valuable for patients with T2DM in Western countries to whom this would also apply.[1,33]

Conclusion

Reducing total salt and its sources had differential associations with ΔHbA1c. However, these associations were dependent on Δcarbohydrate or Δtotal energy intake in men, but independent of either Δcarbohydrate or Δtotal energy intake for Δsalt from miso in women.

Abbreviations

T2DM, type 2 diabetes; HbA1c, hemoglobin A1c; SGLT1, sodium-glucose co-transporter 1; FPG, fasting plasma glucose; PPG, postprandial glucose; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

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Disclosure

The authors report no conflicts of interest in this work.

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