Effects of Sugar-Sweetened Beverage Intake on the Development of Type 2 Diabetes Mellitus in Subjects with Impaired Glucose Tolerance: the Mihama Diabetes Prevention Study

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Summary In Japan, the incidence of type 2 diabetes mellitus (T2DM) is increasing for several reasons, including increased consumption of sugar-sweetened beverages (SSBs). However, whether SSBs cause T2DM by excess of energy production resulting in obesity remains unclear. Therefore, the present study was designed to evaluate the effects of SSB intake on the development of T2DM in subjects with impaired glucose tolerance (IGT). Ninety-three subjects (30 males and 63 females) with IGT aged 40–69 y and residing in the Mihama district (southern Mie Prefecture, Japan) were included in the study. The mean observational period was 3.6 y. All subjects underwent the 75-g oral glucose tolerance test (OGTT) and completed a lifestyle questionnaire survey related to SSB intake. OGTT results and SSB intake were evaluated before and after the observational period. In addition, the correlation between SSB intake and development of T2DM was investigated. Of the 93 subjects, 20 (21.5%) developed T2DM (T2DM group) and demonstrated a significantly high SSB intake compared with the group that did not develop the disease (non-T2DM group). The odds ratio for the incidence of T2DM based on SSB intake was 3.26 (95% confidence interval, 1.17–9.06). The body mass index (BMI; kg/m^2) and the homeostasis model assessment for insulin resistance (HOMA-R) values was significantly higher in the T2DM group than in the non-T2DM group, while the insulinogenic indices were significantly lower in the former than in the latter group. The sum of insulin secretion levels during OGTT was not significantly different between groups. SSB intake correlated with the predisposition for developing T2DM, possibly by influencing body weight, insulin resistance, and the ability of the pancreatic beta cells to effectively compensate for the insulin resistance.

Key Words type 2 diabetes, sugar intake, sweetened beverage, nutritional behavior, cohort study

The incidence of type 2 diabetes mellitus (T2DM) has markedly increased worldwide, particularly in eastern Asia, because of the rapid westernization of traditional lifestyles (1). Because the development of T2DM is gradual, its progression from impaired glucose tolerance (IGT) can be theoretically prevented by lifestyle intervention. According to the findings of several interventional trials, including the Da Qing (2), Finnish (3), and Diabetes Prevention Program (4), lifestyle intervention is associated with a 50% decrease in the incidence of T2DM. A similar trial conducted in Japan demonstrated a 67.4% decrease in the incidence of T2DM after lifestyle intervention (5).

Healthier eating habits, including decreased total fat and saturated fatty acid intake and increased dietary fiber intake, are critical in terms of lifestyle intervention. Specifically, sugar-sweetened beverages (SSBs) are rapidly absorbed in the body and elevate blood glucose levels; therefore, the habitual intake of SSBs is detrimental to health. However, whether SSBs cause T2DM by excess energy production and subsequent obesity remains unclear.

The aim of the present health study was to investigate the risk of T2DM onset in subjects with IGT and habitual SSB intake. In particular, the relationship between SSB

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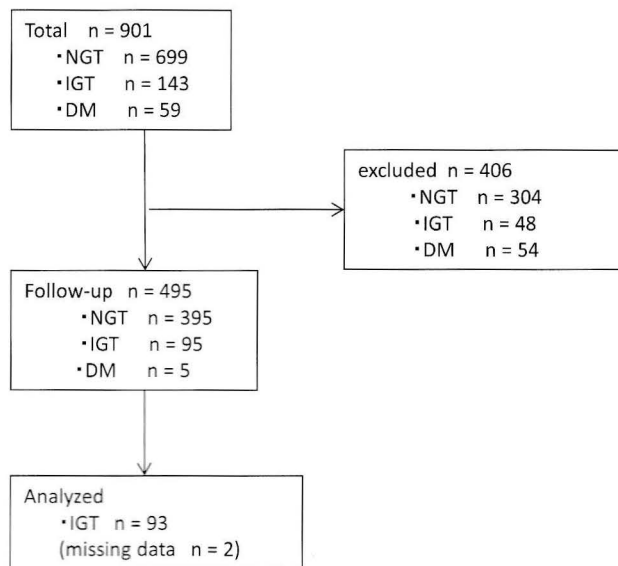E-mail: y-sumida@wh.commufa.jp

Total n = 901
• NGT n = 699
• IGT n = 143
• DM n = 59

excluded n = 406
• NGT n = 304
• IGT n = 48
• DM n = 54

Follow-up n = 495
• NGT n = 395
• IGT n = 95
• DM n = 5

Analyzed
• IGT n = 93
(missing data n = 2)

Fig. 1. Flow chart for subject inclusion.

intake and insulin secretion/sensitivity was investigated.

METHODS

Study design and subjects. This retrospective cohort study was conducted in Mihama, Mie Prefecture, Japan. From 2000 to 2007, 93 subjects (30 males and 63 females) aged 40–69 y that had their first episode of IGT were enrolled and followed up for more than a year (Fig. 1). All subjects underwent a 75-g oral glucose tolerance test (OGTT) and completed a questionnaire survey about diet and exercise habits.

Subjects with a previous diagnosis of or currently undergoing treatment for T2DM and those with severe hepatic or renal disease or a history of gastrectomy were excluded from the study. Subjects receiving anti-hypertensive or hypolipidemic drugs were included in the study. The study protocol was approved by the Ethics Committee of Mie University, Graduate School of Medicine, and adhered closely to the ethical principles of the 1995 Declaration of Helsinki regarding human experimentation (revised in Edinburgh in 2000). Written informed consent was obtained from all subjects after detailed explanation on the study.

Measurements. Height, body weight, and abdominal circumference were measured after overnight fasting and the body mass index (BMI) was calculated. Prior to the OGTT, blood samples were collected to evaluate levels of hemoglobin A1c (HbA1c) and serum lipids [low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides]. The OGTT was performed using Trelan-G75 (75 g of glucose in 225 mL of water; Ajinomoto, Tokyo, Japan). Blood samples were collected at 0, 30, and 120 min after oral glucose loading, and blood glucose and serum insulin (immunoreactive insulin; IRI) levels were evaluated. The homeostasis model assessment for insulin resistance (HOMA-R) values were calculated using fasting plasma glucose (FPG) and insulin levels (6). HbA1c levels were evaluated using the latex agglutination method (Determiner

Table 1. Differences in lifestyle habits between subjects with and without the development of diabetes.

	Questionnaire content	p-value
Exercise	Do you exercise regularly?	0.39
	Regular exercise other than everyday work	0.26
	Do you usually walk more than 30 min/d?	0.90
	How fast do you walk?	0.07
	Do you usually use an elevator	0.67
	How many hours (min) do you walk?	0.48
Smoking	Do you smoke cigarettes?	0.23
	How many cigarettes do you smoke daily?	0.24
	How long have you smoked?	0.11
Rest	Do you suffer from lack of sleep?	0.23
	Do you feel tired?	0.36
	Do you usually communicate?	0.07
	Do you engage in recreational activities?	0.60
	Do you live a regular life?	0.30
	Do you rest regularly?	0.26
	Do you have changes of pace?	0.29

All p-values were calculated using the chi-squared test. A p-value of <0.05 was considered statistically significant.

Table 2. Differences in eating habits between subjects with and without the development of diabetes.

Eating habits	p-value
Meal time	0.995
Eating until the feeling of fullness	0.588
Quantity of animal fat intake	0.388
Seasoning (salt)	0.209
Contents of meals (breakfast and lunch)	0.450
Frequency of eating with meals in a week (more or less three times a week)	
Meat	0.456
Fish	0.151
Soybeans	0.763
Eggs	0.421
Deep-fried food	0.061
Eating out	0.999
Midnight snack	0.141
Alcohol consumption	0.169
Frequency of eating with meals in a day (daily or sometimes or none)	
Vegetables	0.685
Milk and dairy products	0.090
Citrus fruits	0.802
Fruits	0.425
Sweets	0.323
Sugar-sweetened beverages	0.020

All p-values were calculated using the chi-squared test. A p-value of <0.05 was considered statistically significant.

HbA1c; Kyowa Medex, Tokyo, Japan) and expressed as National Glycohemoglobin Standardization Program (NGSP) units as recommended by the Japan Diabetes Society (7). Blood glucose levels were measured using the glucose oxidase method, and IRI levels were mea-

Table 3. Differences in clinical parameters between subjects with and without the development of diabetes (at baseline).

Characteristics and variables	Developed DM		p-value
	(+)	(−)	
Age (y)	56.6±7.1	53.6±7.2	0.109
Body mass index (kg/m²)	24.8±3.5	23.7±3.1	0.142
HbA1c (%)	5.9±0.7	5.7±0.7	0.021
Fasting plasma glucose (mmol/L)	5.9±0.6	5.4±0.6	<0.001
30-min glucose (mmol/L)	10.6±1.1	9.3±1.4	<0.001
120-min glucose (mmol/L)	9.1±1.2	8.6±1.2	0.065
Fasting plasma insulin (pmol/L)	42.0±18.6	33.0±15.0	0.033
30-min insulin (pmol/L)	183.0±105.0	204.0±117.0	0.482
120-min insulin (pmol/L)	307.8±172.2	329.4±176.4	0.625
ΣPG (mmol/L)	25.6±1.5	23.3±2.0	<0.001
ΣIRI (pmol/L)	532.8±253.8	566.4±276.0	0.626
ΔIRI/ΔPG	0.3±0.16	0.5±0.73	0.144
HOMA-R	1.9±0.9	1.3±0.7	0.009

Data are presented as means±SE.

30/120-min glucose, plasma levels of glucose 30/120 min after oral loading of 75 g of glucose; ΣPG, sum of plasma glucose during oral glucose load; ΣIRI, sum of serum immunoreactive insulin levels during oral glucose loading; ΔIRI/ΔPG, insulinogenic index [(30 min. IRI−fasting IRI)(μU/mL)/(30 min. PG−fasting PG)(mg/dL)]; HOMA-R, homeostasis model assessment for insulin resistance [fasting plasma glucose (mg/dL) x fasting serum insulin levels (μU/mL)/405]. All p-values were calculated using the t-test. A p-value of <0.05 was considered statistically significant.

sured using an enzyme immunoassay that employed a specific antibody against human insulin (AIA-PACK IRI; Tosoh Bioscience LLC, Tokyo, Japan). On the basis of the diagnostic criteria for diabetes established by the World Health Organization (8), the subjects were divided into three groups: normal glucose tolerance (NGT), IGT/impaired fasting glucose, and DM (Fig. 1). In addition, a questionnaire regarding past medical history, history of health examinations, subjective symptoms, exercise routines, and smoking habits was completed by all subjects (Table 1).

Development of T2DM from IGT. All subjects underwent an annual OGTT during the entire observation period. The questionnaire responses and laboratory data obtained during the first diagnosis of IGT were designated as the "before observation" data, and those obtained at the end of the observation or at diagnosis of T2DM were designated as the "after observation" data.

Dietary assessment. We used a 19-item questionnaire to assess dietary habits (Table 2). SSBs included canned coffee, carbonated drinks, and juices. The source of sweetness (fructose, glucose, or sucrose) was not differentiated. The subjects were divided into three groups according to the frequency of SSB intake: everyday-intake, occasional-intake, and no-intake groups. For statistical analysis, SSB (+) and SSB (−) groups were created, with the former including the everyday-intake group and the occasional-intake group and the latter including the no-intake group.

Statistical analyses. Student's t-test was used to compare parameters between the T2DM and non-T2DM groups at the end of the observational period, while the chi-squared test was used to compare lifestyle and dietary factors between groups at the end of the obser-

vational period. The relationship between the development of T2DM (dependent variable) and SSB intake at baseline and at the end of the observational period (independent variable) was assessed by logistic analysis. In addition, the influence of age, sex, and duration of observation were analyzed by logistic analysis. A probability (p) value of <0.05 was considered statistically significant. All statistical analyses were performed using JMP version 7 software (SAS Institute Inc., Cary, NC).

RESULTS

There were no significant differences in the responses provided in the questionnaires listed in Table 1 and Table 2, except in regard to the SSB intake between the T2D and non-T2DM groups.

Table 3 lists the characteristics of the subjects divided into two groups according to T2DM development at baseline. HbA1c, FPG, 30-min glucose levels after glucose loading, fasting IRI, ΣPG, and HOMA-R were significantly higher in the T2DM group than in the non-T2DM group.

Table 4 demonstrates the characteristics of the subjects divided into two groups according to the development of T2DM at the end of the observational period. The mean observational period was 3.6±0.2 y. Among the 93 subjects with IGT at baseline, 20 (21.5%) developed diabetes, 33 (33.5%) demonstrated persistent IGT, and 40 (43.0%) of the subjects was on transition to NGT. There were no significant differences in age or observational period between groups. HbA1c, FPG, and 120-min glucose levels after glucose loading were significantly higher in the T2DM group than in the non-T2DM group. Although fasting IRI was higher (p<0.005) in the T2DM group, there was no significant difference in

Table 4. Differences in clinical parameters between subjects with and without the development of diabetes (at the end of the observational period).

Characteristics and variable	Developed DM		p-value
	(+)	(−)	
Number of participants (M/F)	20 (8/12)	73 (22/51)	—
Family history of type 2 diabetes (%)	50.0	45.2	—
Age (y)	59.4±1.5	57.4±0.9	0.279
Observational period (y)	3.5±0.4	3.6±0.2	0.707
Body mass index (kg/m²)	24.7±0.8	22.6±0.4	0.012
HbA1c (%)	6.2±0.09	5.8±0.04	<0.001
Fasting plasma glucose (mmol/L)	6.2±0.2	5.3±0.1	<0.001
30-min glucose (mmol/L)	10.8±0.4	9.0±0.2	<0.001
120-min glucose (mmol/L)	12.4±0.3	7.4±0.2	<0.001
Fasting plasma insulin (pmol/L)	36.0±4.2	26.4±1.8	0.001
30-min insulin (pmol/L)	139.8±12.0	189.0±12.0	0.042
120-min insulin (pmol/L)	334.8±34.8	262.2±19.2	0.078
ΣPG (mmol/L)	29.4±0.6	21.8±0.3	<0.001
ΣIRI (pmol/L)	510.6±42.0	477.6±28.2	0.570
ΔIRI/ΔPG	0.2±0.02	0.4±0.04	0.009
HOMA-R	1.7±0.2	1.1±0.1	0.001

Data are presented as means±SE.
30/120-min glucose, plasma levels of glucose 30/120 min after oral loading of 75 g of glucose; ΣPG, sum of plasma glucose during oral glucose load; ΣIRI, sum of serum immunoreactive insulin levels during oral glucose loading; ΔIRI/ΔPG, insulinogenic index [(30 min. IRI−fasting IRI)(μU/mL)/(30 min. PG−fasting PG)(mg/dL)]; HOMA-R, homeostasis model assessment for insulin resistance [fasting plasma glucose (mg/dL) x fasting serum insulin levels (μU/mL)/405]. All p-values were calculated using the t-test. A p-value of <0.05 was considered statistically significant.
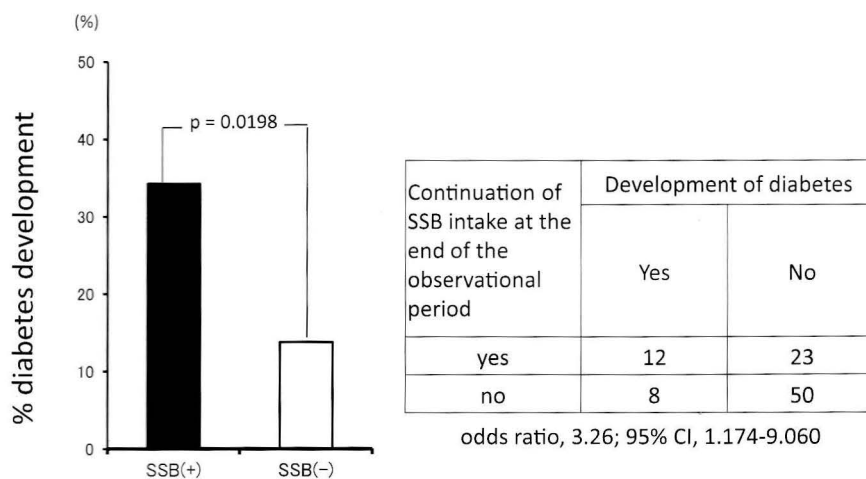

Fig. 2. Bar graph data showing the rate of diabetes development with or without sugar-sweetened beverage (SSB) intake at the end of the observational period. (+) shows SSB intake (black bars), and (−) shows no SSB intake (white bars). p-values are calculated using the chi-squared test. A p-value of <0.05 was considered statistically significant.

the sum of serum insulin levels during glucose loading (ΣIRI) between groups. The insulinogenic index [ΔIRI/Δplasma glucose (PG)] was significantly lower ($p<0.01$) and BMI and HOMA-R were significantly higher ($p<0.05$ and $p<0.005$, respectively) in the T2DM group than in the non-T2DM group. Between the start and end of the observational period, BMI decreased in both groups; however, BMI levels of subjects in the non-T2DM group significantly decreased compared with those of subjects in the T2DM group ($p=0.005$). ΣIRI and HOMA-R decreased in both groups, albeit without any significant difference.

With regard to the rate of development of diabetes from IGT according to the SSB intake at the end of the observational period, among 35 subjects that continued SSB intake, 12 (34.3%) developed diabetes. However, only 8 (13.8%) of the 58 subjects that refrained from SSB intake by the end of the observational period developed diabetes; this difference was statistically significant ($p=0.0198$).

The odds ratio (OR) for the incidence of T2DM based on the SSB intake at the end of the observational period was 3.26 [95% confidence interval (CI)=1.174–9.060; Fig. 2]. The OR for the incidence of diabetes based on SSB intake at baseline was 1.48 (95% CI, 0.548–4.004), but it was not statistically significant. Next, we assessed the incidence of diabetes based on the SSB intake before and at the end of the observational period using a logistic regression model. The OR for the incidence of T2DM at baseline was 1.067 (95% CI, 0.367–3.099), while that at the end of the observational period was 3.20 (95% CI, 1.101–9.305), and it was statistically significant. After adjustment for sex, age, and duration of observation, the OR for the development of T2DM based on the SSB intake at baseline was 1.03 (95% CI, 0.331–3.187), while that at the end of observation was 3.34 (95% CI, 1.106–10.111); the latter was statistically significant.

DISCUSSION

To the best of our knowledge, this is the first study showing the effects of SSB intake on the T2DM incidence and in relation to the insulin secretion after the OGTT. The results indicate that the incidence of diabetes in individuals ingesting SSBs is approximately three-fold higher than individuals with no SSB ingestion. There was a slight correlation between the incidence of diabetes and SSB intake before the observational period. Therefore, it is crucial to consider SSB intake at the end of the observational period because the incidence of diabetes appears to decrease if SSB intake is discontinued.

Previous studies have reported a correlation between body weight gain and SSB intake (9–16). For example, Schulze et al. reported that the relative risk (RR) of T2DM in subjects consuming SSBs more than once a day is 1.83 (95% CI, 1.42–2.36; p<0.01) compared with subjects consuming SSBs less than once a month, while the RR in subjects consuming fruit punch more than once a day was 2.00 (95% CI, 1.33–3.03; p=0.01) compared with subjects ingesting fruit punch less than once a month (9). Moreover, Schulze et al. reported that body weight gain in subjects ingesting SSBs was higher during the observational period than at the beginning of the study and that SSB intake during the observational period was significantly correlated with the risk of T2DM onset (9). The RR in our present study differed from that in previous reports because we included only subjects with confirmed IGT, while healthy subjects were also included in previous studies. The perception of SSBs differs between the Japanese and Westerners. In Western countries, SSBs include soda, but not juice with 100% fruit extract or added sugar and fructose or canned coffee, which is commonly consumed in Japan. Therefore, caution is necessary while interpreting and generalizing data from the West and Japan.

The carbohydrates used to sweeten SSBs primarily include sucrose, fructose, and glucose. Unlike glucose, fructose neither stimulates insulin secretion nor enhances leptin production (14, 17). Because leptin inhibits food intake and increases energy expenditure, the lower leptin concentrations induced by fructose would tend to enhance food intake and decrease energy expenditure (14). Hence, excess fructose intake may induce obesity and adiposity leading to insulin resistance, hyperinsulinemia, and hypertriglycerolemia (14, 18).

The results of the present study suggest that, in subjects with continued SSB intake, a smaller decrease in BMI resulted in lesser changes in HOMA-R, although insulin secretion was unable to completely compensate for the insulin resistance. We think this is one explanation for the development of diabetes from IGT in the Japanese population of the present study.

The monosaccharides in SSBs play an important role in the development of diabetes from IGT. Excess intake of monosaccharides causes body weight gain by enhancing the synthesis of nonesterified fatty acids and inducing insulin resistance (18–20). Fatty acids can directly act on skeletal muscle cells and inhibit insulin-induced glucose uptake, which subsequently increases hepatic glucose flow and output (21, 22). Fatty acids can also inhibit insulin secretion from pancreatic beta cells (23). Elevated blood glucose levels lead to glucose toxicity, which in turn causes insulin resistance and defective insulin secretion. This would be one of the mechanisms of T2DM onset. Malik et al. reported that excessive fructose intake induces T2DM, which is in agreement with our present findings (24).

The average SSB intake in the West is much higher than that in Japan. BMI as a risk factor for T2DM is thought to be lower among the Japanese than among the Westerners (25). Furthermore, insulin secretion after glucose loading is lower in the Japanese population than in the Westerners (25). In this study, the mean BMI of the subjects did not reach the level that induces obesity. Based on these considerations, we believe that our study population developed T2DM because the slight body weight gain after excessive SSB intake induced insulin resistance. The Hisayama study reported that one of the risk factors for T2DM in Japanese men is excess alcohol intake and a decreased polyunsaturated fat to saturated fat (P/S) ratio in Japanese women (26). Because several dietary factors are involved in lifestyle intervention, it is not possible to prevent the development of T2DM if other factors such as alcohol, fat, and SSB intake are not addressed. Further investigations to elucidate the role of dietary factors in the development of diabetes are required to develop an efficient educational program aiming at to prevent IGT progression to diabetes.

The present study has some limitation. First, there was a possible selection bias because some subjects diagnosed with IGT were excluded from the study. Second, the development of T2DM was investigated based on the SSB intake at the beginning and at the end of the observational period. Third, the study was restricted to middle-aged and elderly Japanese individuals living in a rural area (Mihama Town), where there were fewer fast-food outlets compared with those in other districts of Japan. The number of obese individuals was alsp fewer in this area than in other areas of Mie Prefecture. Therefore, our subjects may not effectively represent other

populations. Furthermore, the overall sample size was relatively small.

In the present study, because the intake of SSB was high in T2DM subjects, they had significantly lower weight loss than subjects that did not develop diabetes. This also explains the lack of improvement in insulin resistance. Moreover, the pancreatic beta cells cannot completely compensate for insulin resistance.

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