Habitual Hot-Tub Bathing and Cardiovascular Risk Factors in Patients With Type 2 Diabetes Mellitus: A Cross-Sectional Study

Hisayuki Katsuyama[a, d], Mariko Hakoshima[a], Hiroki Adachi[a], Yoshinori Masui[b], Akahito Sako[b], Shigeko Inokuma[c], Hidekatsu Yanai[a]

Abstract

Background: Several studies suggested that heat therapy, including sauna or hot-tub bathing, was associated with improved glycemia and other risk factors for cardiovascular diseases. This study aimed to assess the influences of the habit of hot-tub bathing on cardiovascular risk factors in patients with type 2 diabetes in a real-world setting.

Methods: In this cross-sectional study, we enrolled the patients with type 2 diabetes who regularly visited the outpatient clinic between October 2018 and March 2019. We obtained the information on the habit of hot-tub bathing by using a self-reported questionnaire. The results of anthropometric measurements, blood tests and medications were obtained from the medical charts. We divided the patients into three groups according to the frequency of hot-tub bathing as follows; group 1: ≥ 4 times a week, group 2: < 4 times a week, ≥ 1 time a week, group 3: < 1 time a week. The biomarkers were compared among the groups by one-way analysis of variance. Multiple linear regression analyses were performed to adjust for confounding variables.

Results: We enrolled 1,297 patients. There were significant differences in body mass index (group1: 25.5 ± 5.0, group 2: 26.0 ± 5.4, group 3: 26.7 ± 6.0, P = 0.025), diastolic blood pressure (73 ± 12, 75 ± 12, 77 ± 13, P = 0.001) and hemoglobin A1c (7.10 ± 0.97, 7.20 ± 1.11, 7.36 ± 1.67, P = 0.012). Multiple regression analysis revealed that the frequency of hot-tub bathing was a significant determinant of hemoglobin A1c, body mass index and diastolic blood pressure.

Conclusions: In this real-world study, habitual hot-tub bathing was associated with slight improvements in glycemia, obesity and diastolic blood pressure, and thus, can be a possible lifestyle intervention in patients with type 2 diabetes.

Keywords: Type 2 diabetes; Hot-tub bathing; Heat; Obesity; Hypertension

Introduction

The epidemic of diabetes mellitus (DM) is one of the critical issues in public health and medical economics. The number of people with DM was estimated to be 415 million worldwide in 2015 and to rise to 642 million by 2040. DM accounted globally for 12.8% of all-cause mortality [1]. Cardiovascular (CV) diseases are the leading cause of morbidity and mortality of patients with type 2 DM (T2DM) [2, 3]. Population-based cohort studies revealed that impaired fasting glucose levels or the presence of glucose tolerance were the risks for CV diseases [4, 5]. The presence of obesity as well as hypertension, hypertriglyceridemia, and/or low high-density lipoprotein cholesterol (HDL-C), were associated with coronary artery diseases (CADs) [6]. Previous large-scale randomized studies, such as Japan Diabetes Outcome Intervention Trial 3 (J-DOIT 3) and Steno-2 suggested that multifactorial interventions for control of glucose, blood pressure, and lipids reduce the occurrences of CV death or CV events in patients with T2DM [7, 8]. Along with pharmacological approaches, lifestyle modification, including healthy diet and increased physical activity, play a crucial role in the prevention of CV diseases in patients with T2DM [9].

Heat therapy, including a sauna or hot-tub bathing, was reported to be a useful therapeutic tool in daily life for T2DM and metabolic diseases. A cohort study in Finland revealed that the frequency of sauna bathing was inversely associated with fatal CV events in middle-aged subjects [10]. Another prospective cohort study from Japan reported that the frequency of hot-tub bathing was beneficially associated with the occurrence of CV diseases [11]. Hot-tub therapy improved glycemic control and reduced body weight in patients with T2DM in a small interventional study [12]. Animal studies suggested that the attenuations of insulin resistance and in-

[a]Department of Diabetes, Endocrinology and Metabolism, National Center for Global Health and Medicine Kohnodai Hospital, Chiba, Japan
[b]Department of Internal Medicine, National Center for Global Health and Medicine Kohnodai Hospital, Chiba, Japan
[c]Department of Rheumatology and Collagen Diseases, National Center for Global Health and Medicine Kohnodai Hospital, Chiba, Japan
[d]Corresponding Author: Hisayuki Katsuyama, Department of Diabetes, Endocrinology and Metabolism, National Center for Global Health and Medicine Kohnodai Hospital, Ichikawa, Chiba 272-8516, Japan.
Email: d-katsuyama@hospk.ncgm.go.jp

flammation by heat stimulation could be involved in the beneficial effects of heat therapy [13]. However, no large-scale studies in the real-world setting examined the effects of hot-tub bathing on CV risk factors in patients with T2DM. In Japan, almost all residences are fitted with a hot-tub and hot-tub bathing is a traditional and common life habit. Thus, Japanese patients with T2DM were considered suitable to test the influences of the daily heat exposure on CV risk factors. We conducted a cross-sectional observational study to investigate the effects of the habit of hot-tub bathing on various CV risk factors in patients with T2DM.

Materials and Methods

Subjects

A cross-sectional study was conducted between October 20, 2018, to March 31, 2019, at the Department of Diabetes, Endocrinology and Metabolism of the National Center for Global Health and Medicine Kohnodai Hospital, Japan. To avoid the seasonal changes in the frequency of habitual hot-tub bathing, we conducted this study only in winter. The inclusion criteria were the patients of 20 years of age or over with T2DM, who regularly visited the outpatient clinic of the hospital and agreed to participate in the study. We excluded the patients with all types of diabetes other than T2DM and those who could not answer the questionnaire, which was used in this study.

Ethical issues and informed consent

This study involves human participants and was approved by the Institutional Ethics Committee of the National Center for Global Health and Medicine (NCGM-G-003043). This trial was registered with the University Hospital Medical Information Network (UMIN) clinical trials registry, number UMIN000035930. All participants were provided clear information about the study and gave written consent prior to enrollment in the study.

Data collection

The information on medications, anthropometric measurements and blood tests was obtained from the medical charts. The information of the habits of hot-tub bathing was collected by using a self-administered questionnaire, which was written in the Japanese language and included items on the frequency and duration of hot-tub bathing, water temperature and the presence of the hot-tub in the residence. Body mass index (BMI) was calculated by body weight in kilograms divided by the square of the height in meters. The results of blood tests included both fasting and postprandial samplings. Plasma glucose was obtained using the hexokinase method. Serum hemoglobin A1c (HbA1c), serum creatinine, serum total cholesterol (TC) and serum triglyceride (TG) were measured by enzymatic assays. Serum low-density lipoprotein-cholesterol (LDL-C)

and serum HDL-C were determined by a direct method. Serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), and serum γ-glutamyl transferase (γGTP) were measured by the Japan Society of Clinical Chemistry transferable method. Estimated glomerular filtration rate (eGFR) was calculated using the following formula: eGFR = 194 × (serum creatinine - 1.094) × (age - 0.287) × 0.739 [14]. The results of the blood tests included both fasting and postprandial samplings, which were obtained on the same day or within 2 months before or after the day of the questionnaire.

Risk factors for CV diseases

In this study, we considered systolic blood pressure, diastolic blood pressure, BMI, plasma glucose, HbA1c, TC, TG, LDL-C, HDL-C, eGFR as possible CV risk factors [15, 16].

Statistics

Pearson's simple correlation coefficients were calculated to determine the correlations between the data from the anthropometric measurements and blood tests and the frequency of hot-tub bathing. We divided the patients into three groups according to the frequency of hot-tub bathing as follows; group 1: ≥ 4 times a week, group 2: < 4 times a week, ≥ 1 time a week, group 3: < 1 time a week. Comparisons of variables between the three groups were performed by one-way analysis of variance (ANOVA) and Tukey's multiple comparison test. Pearson's Chi-squared test (χ^2) was applied to categorize variables. Multiple linear regression analysis was performed to identify the predictors included in the multivariable analysis. The variables selected for the multivariate regression analysis were based on the statistical significance (P < 0.05) of univariate regression analysis, including age, gender, BMI, systolic blood pressure, ALT, HDL-C, LDL-C, TG, eGFR, HbA1c, insulin use, number of hypoglycemic agents, number of hypolipidemic agents, number of antihypertensive agents and frequency of hot-tub bathing. Multicollinearity was checked by a variance inflation factor (< 2). All data are expressed as mean ± standard deviation (SD). P value < 0.05 was considered statistically significant. Statistical analysis was done using SPSS version 23 (IBM, USA).

Results

Baseline characteristics of the patients

We collected the answer of the questionnaire from 1,304 patients. Among them, four patients were excluded since they had type 1 and other types of diabetes. We also excluded three patients due to lack of the data. Thus, 1,297 patients with T2DM were enrolled in this study.

The baseline clinical characteristics of the patients are presented in Table 1. The mean age of the study participants was 66.9 ± 13.6 years, the mean BMI was 25.9 ± 5.3 kg/m^2, the

Table 1. The Clinical and Laboratory Characteristics of the Enrolled Patients

Variables	Data obtained (n)	Mean ± SD, n (%)
N	1,297	1,297
Gender (male)	1,297	713 (55%)
Age (years)	1,297	66.9 ± 13.6
Body height (cm)	1,183	161 ± 10
Body weight (kg)	1,221	67.1 ± 16.5
BMI (kg/m^2)	1,160	25.9 ± 5.3
Waist circumference (cm)	262	94 ± 15
Systolic blood pressure (mm Hg)	984	133 ± 16
Diastolic blood pressure (mm Hg)	979	74 ± 12
Plasma glucose (mg/dL)	1,230	157 ± 53
HbA1c (%)	1,275	7.17 ± 1.14
AST (IU/L)	1,234	27 ± 14
ALT (IU/L)	1,220	28 ± 23
γGTP (IU/L)	1,052	43 ± 71
Total cholesterol (mg/dL)	983	185 ± 35
HDL-C (mg/dL)	1,215	55 ± 15
LDL-C (mg/dL)	795	104 ± 27
Triglyceride (mg/dL)	1,224	151 ± 122
eGFR (mL/min/1.73 m^2)	1,209	70 ± 22
History of coronary artery diseases	1,297	86 (7%)
History of cerebral infarction	1,297	71 (5%)
Result of questionnaire		
Frequency of hot-tub bathing (times/week)	1,297	4.2 ± 2.7
Duration of hot-tub bathing (min)	1,168	16 ± 14
Presence of hot-tub in residence (yes)	1,115	1,114 (99.9%)

BMI: body mass index; HbA1c: hemoglobin A1c; AST: aspartate aminotransferase; ALT: alanine aminotransferase; γGTP: γ-glutamyl transferase; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; eGFR: estimated glomerular filtration rate; SD: standard deviation.

mean systolic blood pressure was 133 ± 16 mm Hg, the mean diastolic blood pressure was 74 ± 12 and the mean HbA1c was 7.17±1.14%. The mean frequency of hot-tub bathing was 4.2 ± 2.7 times a week and the mean duration of hot-tub bathing was 16 ± 14 min. Eighty-six patients (6.6%) had a past history of CAD and 71 patients (5.5%) had a history of cerebral infarction.

Table 2 shows the medications of the patients. Two hundred one patients (15.5%) used insulin, whereas 188 patients (14.5%) took no medication for diabetes. Among the hypoglycemic agents, dipeptidyl peptidase-4 (DPP-4) inhibitors were mostly used (61.4%), followed by metformin (43.1%) and sodium-glucose cotransporter 2 (SGLT2) inhibitors (24.1%). About 57.1% of patients were given antihypertensive agents. The most prescribed drug for hypertension was angiotensin II receptor blockers (45.6%), followed by calcium channel blockers (39.4%). 63.1% of patients received hypolipidemic agents. The most prescribed drug for dyslipidemia was statins (52.4%) followed by ezetimibe (11.6%) and fibrates (4.3%). Antiplatelet drugs were prescribed in 189 patients (14.6%).

Correlations between frequency of the hot-tub bathing and metabolic parameters

Pearson's simple correlations showed weak inverse correlations between frequency of hot-tub bathing and body weight (R = -0.089, P = 0.002), BMI (R = -0.104, P < 0.001), waist circumference (R = -0.165, P = 0.014), diastolic blood pressure (R = -0.118, P < 0.001), plasma glucose (R = -0.080, P = 0.005) and HbA1c (R = -0.078, P = 0.005) (Table 3). There was a positive correlation between the frequency of hot-tub bathing and age. The frequency of hot-tub bathing had no significant correlations with systolic blood pressure, AST, ALT, γGTP, TC, HDL-C, LDL-C, TG and eGFR.

The differences in metabolic parameters according to the frequency of hot-tub bathing

The differences in patient characteristics and medications among

Table 2. The Baseline Medications for Diabetes, Hypertension and Dyslipidemia in the Enrolled Patients

Medications, number of medications	N (%), mean ± SD
Medications for diabetes	
Insulin	201 (15.5%)
Metformin	559 (43.1%)
Sulfonylurea	160 (12.3%)
Glinides	72 (5.6%)
Thiazolidinedione	261 (20.1%)
Alpha-glucosidase inhibitors	204 (15.7%)
DPP-4 inhibitors	796 (61.4%)
SGLT2 inhibitors	312 (24.1%)
GLP-1 receptor agonists	115 (8.9%)
No medication for diabetes	188 (14.5%)
Number of hypoglycemic agents	2.1 ± 1.4
Medication for hypertension	
ACE inhibitors	9 (0.7%)
Angiotensin II receptor blockers	591 (45.6%)
Calcium channel blockers	511 (39.4%)
Diuretics	103 (7.9%)
Alpha blockers	16 (1.2%)
Beta blockers	58 (4.5%)
No medication for hypertension	557 (42.9%)
Number of antihypertensive agents	1.0 ± 1.1
Medication for dyslipidemia	
Statins	680 (52.4%)
Ezetimibe	151 (11.6%)
Fibrates	56 (4.3%)
No medication for dyslipidemia	478 (36.9%)
Number of hypolipidemic agents	1.7 ± 0.8
Antiplatelet drugs	189 (14.6%)

DPP-4: dipeptidyl peptidase-4; SGLT2: sodium-glucose cotransporter 2; GLP-1: glucagon-like peptide-1; ACE: angiotensin-converting enzyme; SD: standard deviation.

Table 3. Pearson's Simple Correlations Between the Frequency of Hot-Tub Bathing and Metabolic Parameters

	R	P
Age (years)	0.098	< 0.001
Body weight (kg)	-0.089	0.002
BMI (kg/m^2)	-0.104	< 0.001
Waist circumference (cm)	-0.165	0.014
Systolic blood pressure (mm Hg)	-0.049	0.127
Diastolic blood pressure (mm Hg)	-0.118	< 0.001
Plasma glucose (mg/dL)	-0.080	0.005
HbA1c (%)	-0.078	0.005
AST (IU/L)	0.022	0.441
ALT (IU/L)	0.008	0.771
γGTP (IU/L)	-0.045	0.144
Total cholesterol (mg/dL)	-0.005	0.868
HDL-C (mg/dL)	0.007	0.795
LDL-C (mg/dL)	0.014	0.693
Triglyceride (mg/dL)	-0.037	0.192
eGFR (mL/min/1.73 m^2)	0.026	0.360

BMI: body mass index; HbA1c: hemoglobin A1c; AST: aspartate aminotransferase; ALT: alanine aminotransferase; γGTP: γ-glutamyl transferase; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; eGFR: estimated glomerular filtration rate.

Furthermore, HbA1c (group 1: 7.10 ± 0.97, group 2: 7.20 ± 1.11, group 3: 7.36 ± 1.67, P = 0.012) and diastolic blood pressure (group 1: 73 ± 12, group 2: 75 ± 12, group 3: 77 ± 13, P = 0.001) were significantly lower in the order of group 1, group 2 and group 3. γGTP was higher in group 3 (group 1: 41 ± 47, group 2: 40 ± 49, group 3: 56 ± 144, P = 0.048). There were no significant differences in systolic blood pressure, AST, ALT, total cholesterol, HDL-C, LDL-C, TG and eGFR.

Multiple regression analysis

Table 6 shows the variables independently associated with HbA1c, diastolic blood pressure and BMI in multiple regression analysis. Along with ALT, LDL-C, insulin use, number of hypoglycemic agents, the frequency of hot-tub bathing was a significant determinant of HbA1c (standardized β: -0.078, P = 0.020) (Table 6) after adjusting by age, gender, and the statistically significant variable in the univariate regression analysis. The frequency of hot-tub bathing was independently associated with diastolic blood pressure (standardized β: -0.110, P = 0.006) (Table 6). An independent association was also observed between the frequency of hot-tub bathing and BMI (standardized β: -0.074, P = 0.012) (Table 6).

Discussion

In this study, we examined the influences of hot-tub bathing

the three patient groups divided by the frequency of hot-tub bathing are provided in Table 4. There was only a significant difference in age (group 1: 67.5 ± 13.2, group 2: 68.0 ± 13.6, group 3: 62.3 ± 13.7, P < 0.001), but not in gender, history of CADs, history of cerebral infarction and duration of hot-tub bathing. The rate of prescription of glucagon-like peptide-1 (GLP-1) receptor agonists was higher in the order of group 3 (13.2%), group 2 (9.4%) and group 1 (7.4%). There were no significant differences in other medications for diabetes, hypertension and dyslipidemia, as well as antiplatelet drugs.

Table 5 shows the comparisons of metabolic parameters among three patient groups. Body weight (group 1: 66.2 ± 15.6, group 2: 67.1 ± 16.9, group 3: 70.0 ± 18.6, P = 0.026) and BMI (group 1: 25.5 ± 5.0, group 2: 26.0 ± 5.4, group 3: 26.7 ± 6.0, P = 0.025) were lower in the group with frequent hot-tub bathing.

Table 4. The Comparisons of Patient Characteristics and Medications Among Three Groups Divided by the Frequency of Hot-Tub Bathing

Frequency of hot-tub bathing (per week)	≥ 4 (Group 1)	< 4, ≥ 1 (Group 2)	< 1 (Group 3)	P
N (gender: M/F)	693 (386/307)	415 (235/180)	189 (92/97)	0.163
Age (years)	67.5 ± 13.2	68.0 ± 13.6	62.3 ± 13.7	< 0.001
History of coronary artery diseases	44 (6.3%)	26 (6.3%)	16 (8.5%)	0.547
History of cerebral infarction	45 (6.5%)	19 (4.6%)	7 (3.7%)	0.204
Duration of hot-tub bathing (min)	16 ± 11	16 ± 14	15 ± 13	0.617
Medications for diabetes				
Insulin	101 (14.6%)	73 (17.6%)	27 (14.3%)	0.359
Metformin	287 (41.4%)	185 (44.6%)	87 (46.0%)	0.399
Sulfonylurea	81 (11.7%)	59 (14.2%)	24 (12.7%)	0.339
Glinides	40 (5.8%)	24 (5.8%)	8 (4.2%)	0.693
Thiazolidinedione	140 (20.2%)	88 (21.2%)	33 (17.5%)	0.566
Alpha-glucosidase inhibitors	114 (16.5%)	67 (16.1%)	23 (12.2%)	0.344
DPP-4 inhibitors	417 (60.2%)	273 (65.8%)	104 (55.0%)	0.098
SGLT2 inhibitors	157 (22.7%)	104 (25.1%)	51 (27.0%)	0.394
GLP-1 receptor agonists	51 (7.4%)	39 (9.4%)	25 (13.2%)	0.038
No medication for diabetes	112 (16.2%)	47 (11.3%)	29 (15.3%)	0.081
Number of hypoglycemic agents	2.0 ± 1.4	2.2 ± 1.5	2.0 ± 1.4	0.078
Medication for hypertension				
ACE inhibitors	4 (0.6%)	3 (0.7%)	2 (1.1%)	0.776
Angiotensin II receptor blockers	311 (44.9%)	202 (48.7%)	78 (41.3%)	0.206
Calcium channel blockers	279 (40.3%)	169 (40.7%)	63 (33.3%)	0.180
Diuretics	53 (7.6%)	37 (8.9%)	13 (6.9%)	0.634
Alpha blockers	10 (1.4%)	6 (1.4%)	0 (0%)	0.251
Beta blockers	35 (5.1%)	18 (4.3%)	5 (2.6%)	0.361
No medication for hypertension	294 (42.4%)	170 (41.0%)	93 (49.2%)	0.152
Number of antihypertensive agents	1.0 ± 1.0	1.1 ± 1.0	1.0 ± 1.0	0.090
Medication for dyslipidemia				
Statins	355 (51.2%)	217 (52.3%)	108 (57.1%)	0.352
Ezetimibe	83 (12.0%)	54 (13.0%)	14 (7.4%)	0.127
Fibrates	33 (4.8%)	15 (3.6%)	8 (4.2%)	0.660
No medication for dyslipidemia	261 (37.7%)	154 (37.1%)	63 (33.3%)	0.545
Number of hypolipidemic agents	0.79 ± 0.73	0.81 ± 0.75	0.80 ± 0.68	0.887
Antiplatelet drugs	100 (14.4%)	65 (15.7%)	24 (12.7%)	0.542

DPP-4: dipeptidyl peptidase-4; SGLT2: sodium-glucose cotransporter 2; GLP-1: glucagon-like peptide-1; ACE: angiotensin-converting enzyme; M: male; F: female.

on CV risk factors in patients with T2DM. The results showed that the frequency of hot-tub bathing was associated with lower BMI, diastolic blood pressure and HbA1c, which were retained even after adjusting by age, gender, and other confounding factors. It suggested that the habits of hot-tub bathing were associated with slight improvements in BMI, glycemic control, and diastolic blood pressure.

The energy expenditure in daily life could influence various metabolic factors in patients with T2DM. Non-exercise activity thermogenesis (NEAT) describes the energy expended for everything in the daily business except for sleeping, eating or sport-like exercise. NEAT includes various activities in daily life, such as going to work, housework, as well as bathing and showering [17, 18]. Previous studies reported that NEAT was beneficially associated with insulin resistance, waist circumference, glucose metabolism, blood pressure, and the degree of diabetic nephropathy and neuropathy in patients with T2DM, suggesting that NEAT improves various CV risk fac-

Table 5. The Comparisons of Metabolic Parameters Among Three Groups Divided by the Frequency of Hot-Tub Bathing

Frequency of hot-tub bathing (per week)	≥ 4 (Group 1)	< 4, ≥ 1 (Group 2)	< 1 (Group 3)	P
N (gender: M/F)	693 (386/307)	415 (235/180)	189 (92/97)	0.163
Age (years)	67.5 ± 13.2	68.0 ± 13.6	62.3 ± 13.7	< 0.001
Body weight (kg)	66.2 ± 15.6	67.1 ± 16.9	70.0 ± 18.6	0.026
BMI (kg/m^2)	25.5 ± 5.0	26.0 ± 5.4	26.7 ± 6.0	0.025
Waist circumference (cm)	92 ± 14	94 ± 16	101 ± 17	0.012
Systolic blood pressure (mm Hg)	133 ± 15	132± 18	134 ±17	0.412
Diastolic blood pressure (mm Hg)	73 ± 12	75 ± 12	77 ± 13	0.001
Plasma glucose (mg/dL)	153 ± 50	160 ± 54	162 ± 62	0.057
HbA1c (%)	7.10 ± 0.97	7.20 ± 1.11	7.36 ± 1.67	0.012
AST (IU/L)	27 ± 14	25 ± 12	28 ± 32	0.090
ALT (IU/L)	28 ± 21	26 ± 22	29 ± 30	0.147
γGTP (IU/L)	41 ± 47	40 ± 49	56 ± 144	0.048
Total cholesterol (mg/dL)	185 ± 33	183 ± 35	190 ± 42	0.179
HDL-C (mg/dL)	55 ± 15	56 ± 16	55 ± 16	0.855
LDL-C (mg/dL)	102 ± 32	106 ± 36	112 ± 36	0.431
Triglyceride (mg/dL)	148 ± 125	183 ± 35	190 ± 42	0.275
eGFR (mL/min/1.73 m^2)	70 ± 22	69 ± 21	69 ± 24	0.424

Comparisons of variables between the three groups were performed by one-way analysis of variance (ANOVA) and Tukey's multiple comparison test. Data are expressed as mean ± SD. BMI: body mass index; HbA1c: hemoglobin A1c; AST: aspartate aminotransferase; ALT: alanine aminotransferase; γGTP: γ-glutamyl transferase; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; eGFR: estimated glomerular filtration rate; SD: standard deviation; M: male; F: female.

tors and plays a protective role against diabetic complications [18-20]. In the sub-analyses, body weight and waist circumference were lower in female patients with T2DM [21], who took a bath or shower almost every day, which agreed with the present study.

The improvement in obesity was already reported in a randomized controlled trial. In middle-aged and older adults, 3-month intervention with hot-tub bathing along with diet and exercise reduced body weight, BMI, waist circumference and body fat [22]. Furthermore, our study also showed that the habits of hot-tub bathing were correlated with better glycemia. A previous study reported that a 3-week hot-tub therapy in eight patients with T2DM lowered fasting plasma glucose and HbA1c [12].

Although a cross-sectional study from Japan reported that the time spent in the hot-tub was inversely correlated with the serum TG level [23], we did not observe any significant relationships between the frequency of hot-tub bathing and serum lipids in the present study. The blood tests in our study included both fasting and postprandial blood sampling, and 63% of studied patients took medications for lipidemia, which might affect our results.

In our study, diastolic blood pressure was lower in the patients with frequent hot-tub bathing. The effects of hot-tub bathing on vascular function were already reported in a previous study [24]. The 8-week hot-tub therapy increased flow-mediated vasodilatation, and reduced arterial stiffness mean arterial and diastolic blood pressure, and carotid intima media thickness in young sedentary subjects. Interestingly, in this study, only diastolic blood pressure, not systolic blood pressure, was significantly reduced by the hot-tub therapy, which agreed with the findings of our study. A previous cohort study suggested that in the younger generation, diastolic blood pressure was a stronger predictor of CV diseases compared with systolic blood pressure [25]. In the sub-analyses of our study, a significant reduction of diastolic blood pressure was observed only in patients with age below 65 years. The hypotensive effects of hot-tub bating could lead to a reduction in CV diseases, particularly in younger patients.

A cohort study from Finland revealed that the habit of sauna bathing was associated with lower incidences of CV diseases [10]. Moreover, a recent prospective cohort study from Japan reported that the frequency of hot-tub bathing was inversely correlated with the occurrence of CV diseases, coronary heart diseases and strokes in middle-aged Japanese subjects during 538,373 person-year follow-up, which supplied evidence of the protective effects of hot-tub bathing against CV diseases [11]. These findings, along with our results, suggested that the multifactorial effects of hot-tub bathing against CV risk factors could prevent CV diseases.

Heat stimulation by hot-tub bathing induces nitric oxide (NO) production and increment in blood flow. NO elevation leads to the upregulation of heat shock protein 70 (HSP 70) [13, 26]. The upregulation of HSP 70 enhances the phosphorylation of endothelial nitric oxide synthase (eNOS), which, in turn, elevates insulin signaling and glucose uptake by the skeletal muscle [27]. It was reported that prostacyclin analog administration, which enhances eNOS phosphorylation, might improve insulin

Table 6. The Results of Multiple Regression Analysis, Which Showed Variables Independently Associated With HbA1c, Diastolic Blood Pressure and BMI

Independent variables	β	SE	Standardized β	P
Analysis with HbA1c as the dependent variable[a]				
Gender	0.023	0.083	0.009	0.784
Age	0.006	0.003	0.065	0.098
BMI	-0.001	0.009	-0.003	0.946
ALT	0.008	0.002	0.139	< 0.001
HDL-C	0.003	0.003	0.035	0.339
LDL-C	0.007	0.001	0.179	< 0.001
Triglyceride	0.001	0.000	0.072	0.044
Insulin use	0.609	0.117	0.186	< 0.001
Number of hypoglycemic agents	0.307	0.030	0.363	< 0.001
Frequency of hot-tub bathing (per week)	-0.036	0.015	-0.078	0.020
Analysis with diastolic blood pressure as the dependent variable[b]				
Gender	4.331	0.998	0.178	< 0.001
Age	-0.206	0.046	-0.222	< 0.001
BMI	0.205	0.111	0.087	0.066
ALT	0.041	0.026	0.071	0.113
HDL-C	0.031	0.037	0.038	0.396
LDL-C	0.039	0.016	0.099	0.016
Triglyceride	0.001	0.004	0.007	0.865
eGFR	0.053	0.025	0.094	0.035
Insulin use	- 1.412	1.279	-0.044	0.270
Frequency of hot-tub bathing	- 0.502	0.183	-0.110	0.006
Analysis with BMI as the dependent variable[c]				
Gender	-1.204	0.314	-0.115	< 0.001
Age	-0.129	0.014	-0.323	< 0.001
Diastolic blood pressure	0.027	0.014	0.062	0.050
ALT	0.044	0.008	0.185	< 0.001
HDL-C	-0.075	0.011	-0.212	< 0.001
Triglyceride	0.001	0.001	0.028	0.382
Number of hypoglycemic agents	0.316	0.118	0.086	0.008
Number of hypolipidemic agents	-0.034	0.209	-0.005	0.870
Number of antihypertensive agents	0.818	0.152	0.160	< 0.001
Frequency of hot-tub bathing	-0.144	0.057	-0.074	0.012

[a]Multiple regression analysis with HbA1c as the dependent variable. (R = 0.521, P < 0.001). [b]Multiple regression analysis with diastolic blood pressure as the dependent variable. (R = 0.453, P < 0.001). [c]Multiple regression analysis with BMI as the dependent variable. (R = 0.562, P < 0.001). β: coefficient; SE: standard error; BMI: body mass index; HbA1c: hemoglobin A1c; ALT: alanine aminotransferase; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; eGFR: estimated glomerular filtration rate.

sensitivity in obese patients with T2DM [28]. The upregulation of HSP70 also suppresses inflammatory cytokines, which relates to the improvement of insulin sensitivity and low-grade inflammation [13]. Interestingly, exercise also upregulates HSP70 in skeletal muscle and eNOS in the artery, which could relate to the beneficial metabolic effects of exercise [29].

It was also suggested that hot-tub bathing might improve

glycemia by enhancing insulin secretion. Experiments revealed that temperature elevation activated transient receptor potential melastatin 2 (TRPM2), which is a thermosensitive Ca^{2+}-permeable non-selective cation channel expressed in β-cells, and increased glucose-induced insulin secretion from β-cells [30]. Nevertheless, there were no animal or human studies, which examined the effects of heat therapy on insulin

secretion.

In Japan, it was reported that sudden bath-related deaths occur frequently, particularly among elderly people in winter [31]. Drowning was considered to be the main cause of death, but circulatory system diseases might be the underlying pathophysiology [32]. A cohort study reported that there were no associations between the frequency of hot-tub bathing and the risk of sudden cardiac death or subarachnoid hemorrhage in the middle-aged subjects, suggesting the safety of hot-tub bathing in this population [11]. However, the indication of the hot-tub therapy should be carefully considered in elderly patients.

As shown in Tables 3-6, it is of note that the effect sizes of hot-tub bathing on BMI, diastolic blood pressure and HbA1c were small. A meta-analysis revealed that exercise decreased HbA1c by 0.66% [33]. It was also reported that exercise decreased systolic blood pressure by 2 - 5 mm Hg and diastolic blood pressure by 1 - 4 mm Hg [34]. A cohort study based on 20-year observations revealed that subjects with high physical activity gained 2.6 - 6.2 kg less weight gain than the subjects with low physical subjects [35]. In our study, the effect sizes of hot-tub bathing on diastolic blood pressure and BMI were equivalent, whereas the difference in HbA1c was smaller. Overall, physical activity could lead to multifactorial improvements in CV risk factors, but the effect sizes were small, which agreed with the results of this study.

Previous studies reported reductions in the incidence of CV events with the treatments of SGLT2 inhibitors, GLP-1 receptor agonists and statins [36-39]. Furthermore, it was also reported that SGLT2 inhibitors and GLP-1 receptor agonists contributed to multifactorial improvements in body weight, glycemic control, hypertension, and dyslipidemia [38, 40, 41]. In the current study, there were no significant differences in the rate of prescription of SGLT2 inhibitors and statins, whereas the rate of GLP-1 receptor agonist prescription was significantly lower in the patient group with frequent hot-tub bathing. Despite the lower use of GLP-1 receptor agonists, BMI, diastolic blood pressure and HbA1c were lower in the group with frequent hot-tub bathing. Thus, we considered that the influences of these drugs on our results were limited.

The strength of our study was the great number of subjects based on real-world data. The present study has several limitations. First, due to the nature of the cross-sectional study, we cannot guarantee causality. Second, we could not exclude possible influences from other activities and life habits. The patients, who took a bath frequently, might be more physically active. Indeed, our previous study suggested that the degree of NEAT was greater in patients who take a bath or shower frequently [21]. Third, the results might have been affected by medications or comorbidities. Fourth, we did not consider the influences of other types of bathing, such as showering and sauna. Fifth, the presence or absence of hot-tub in the residence might influence the results. However, as shown in Table 2, almost all of the patients answered that their residences had a hot-tub. Sixth, since we obtained the data from the medical chart, there were lack of data, which might affect the result. To overcome the limitations, further prospective studies such as a randomized controlled trial or a crossover trial will be needed to confirm the beneficial effects of hot-tub bathing on CV risk factors.

Conclusions

Our real-world study suggested that habitual hot-tub bathing leads to small improvements in obesity, diastolic blood pressure and glycemic control, which could support insights obtained from previous studies. Thus, hot-tub therapy could be an auxiliary therapeutic option for patients with T2DM for the prevention of CV diseases.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

All subjects provided written informed consent prior to enrollment in the study.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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