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ORIGINAL

Relation between HOMA-IR and insulin sensitivity index determined by hyperinsulinemic-euglycemic clamp analysis during treatment with a sodium-glucose cotransporter 2 inhibitor

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Abstract. We had aimed to determine whether homeostasis model assessment–insulin resistance (HOMA-IR) reflects insulin resistance-sensitivity during treatment with a sodium-glucose cotransporter 2 inhibitor (SGLT2i). Hyperinsulinemic-euglycemic clamp analysis was performed in 22 patients with type 2 diabetic patients taking dapagliflozin (5 mg/day before or after breakfast). Propensity score matching of these individuals (SGLT2i group) for age, sex, body mass index, and clamp-derived tissue glucose uptake rate with 44 type 2 diabetic patients who had undergone clamp analysis without SGLT2i treatment (control group) identified 17 paired subjects in each group for further analysis of the relation between HOMA-IR and a clamp-derived insulin sensitivity index (ISI). Natural log–transformed HOMA-IR was negatively correlated with ISI in both SGLT2i (r = –0.527, p = 0.030) and control (r = –0.534, p = 0.027) groups. The simple regression lines for log-transformed HOMA-IR and ISI in the two groups showed similar slopes but differed in their intercepts. Multivariate analysis revealed that HOMA-IR for patients with the same ISI in the two groups was related by the formula: $\text{HOMA-IR}_{\text{control}} = \text{HOMA-IR}_{\text{SGLT2i}} \times 2.45$. In conclusion, HOMA-IR was well correlated with ISI during SGLT2i treatment, but values corresponding to the same ISI were lower in the SGLT2i group than in the control group.

Key words: Homeostasis model assessment–insulin resistance (HOMA-IR), Sodium-glucose cotransporter 2 (SGLT2) inhibitor, Hyperinsulinemic-euglycemic clamp, Insulin sensitivity, Insulin resistance

HOMEOSTASIS MODEL ASSESSMENT–INSULIN RESISTANCE (HOMA-IR), which is calculated from circulating glucose and insulin concentrations after fasting, has been shown to reflect well insulin resistance or sensitivity determined by hyperinsulinemic-euglycemic clamp analysis, a gold standard for assessment of insulin resistance-sensitivity [1-3]. Although updated HOMA models such as homeostasis model assessment of insulin sensitivity (HOMA2-%S) [4] and interactive 24-variable homeostasis model of assessment (iHOMA2) have been developed [5], they require complex calculations for their determination. HOMA-IR is thus still applied for the evaluation of insulin resistance-sensitivity in a wide range of settings [6-11].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors administered as hypoglycemic agents have been found to have various additional beneficial clinical effects, including prevention of cardiovascular events and the preservation of renal function [12-16]. SGLT2 inhibitors exert their hypoglycemic effect primarily by promoting urinary glucose excretion, but they appear to trigger a vari-

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ety of secondary effects on hormonal or metabolic status. These latter effects include elevation of the circulating level of glucagon [17, 18] and an increase in hepatic glucose output [17-19] as well as stimulation of lipolysis and a consequent increase in circulating levels of nonesterified fatty acids [18, 20-22]. Given that such hormonal and metabolic changes might affect insulin resistance-sensitivity, it has remained unknown whether HOMA-IR accurately reflects insulin resistance-sensitivity in individuals treated with SGLT2 inhibitors. We therefore investigated whether HOMA-IR indeed reflects insulin resistance-sensitivity as determined by hyperinsulinemic-euglycemic clamp analysis in patients undergoing treatment with an SGLT2 inhibitor.

Materials and Methods

Subjects

Twenty-two subjects (SGLT2 inhibitor group) were recruited from type 2 diabetes patients attending Kobe University Hospital between September 2017 and August 2018. These subjects were selected from individuals aged 20 to 75 years who had been treated with the same antidiabetic, antihypertensive, or lipid-lowering medications for >3 months, had a controlled fasting blood glucose level of <140 mg/dL, and were judged by their attending physician to require treatment with dapagliflozin. Exclusion criteria included: (1) previous treatment with dapagliflozin or other SGLT2 inhibitors, (2) a diagnosis of type 1 diabetes (including slowly progressive type 1 diabetes) or other types of diabetes, (3) actual or possible pregnancy or breastfeeding, (4) the presence of antibodies to insulin that might influence variability of plasma glucose levels, (5) participation in other clinical studies, (6) severe liver dysfunction (serum aspartate aminotransferase or alanine aminotransferase level of ≥2 times the normal upper limit), (7) renal dysfunction (estimated glomerular filtration rate of <50 mL min^{-1} 1.73 m^{-2}), (8) severe cardiac dysfunction (New York Heart Association classification stage of >II), (9) treatment with pioglitazone, long-acting insulin, a long-acting glucagon-like peptide–1 receptor agonist, or a once-weekly dipeptidyl peptidase–4 inhibitor, (10) allergy to insulin, (11) frequently recurring severe hypoglycemia or hospitalization due to serious hypoglycemia or diabetic ketoacidosis within the previous year, (12) a psychiatric disorder, (13) contraindication for dapagliflozin, (14) treatment with other medications that affect glucose metabolism (such as beta-blockers, corticosteroids, or monoamine oxidase inhibitors), and (15) a judgment of ineligibility to participate by researchers for any other reason.

Forty-four type 2 diabetic patients who did not fulfill any of the above exclusion criteria and had undergone hyperinsulinemic-euglycemic clamp analysis at Kobe University Hospital between October 2008 and April 2018 were selected as controls. The 22 patients in the SGLT2 inhibitor group and 44 patients in the control group were matched for age, sex, body mass index, and tissue glucose uptake rate (TGUR) on the basis of the logit of the propensity score with the use of the nearest-neighbor matching method without replacement at a caliper width of SD × 0.3.

This study was conducted in accordance with the Declaration of Helsinki and its amendments and was approved by the Ethics Committee of Kobe University Hospital (approval number 180155). All participants provided written informed consent.

Glucose clamp analysis

For patients in the SGLT2 inhibitor group, a hyperinsulinemic-euglycemic clamp was performed within 6 days after the start of dapagliflozin treatment (5 mg/day before or after breakfast) with the use of an artificial endocrine pancreas (STG-22 or -55; Nikkiso, Shizuoka, Japan). All antidiabetic medications with the exception of dapagliflozin were withheld on the morning of the analysis. Details of the clamp technique were described previously [23, 24]. In brief, regular insulin was administered continuously by intravenous infusion at a rate of 40 mU/m^2/min to ensure a plasma insulin concentration of 100 μU/mL. To correct for the influence of urinary glucose excretion, we applied a modification of DeFronzo's method [17]: Subjects in the SGLT2 inhibitor group were thus instructed to void before and soon after the glucose clamp, and urinary glucose excretion was then calculated from the volume and glucose concentration of the second voided urine sample. The urinary glucose excretion rate was obtained by dividing urinary glucose excretion by the duration of the clamp (120 min). TGUR was calculated by subtraction of the urinary glucose excretion rate from the mean glucose infusion rate (GIR, mg/kg/min) during the final 30 min of the glucose clamp [17]. An index of insulin sensitivity (ISI) derived from the hyperinsulinemic-euglycemic clamp analysis was obtained by dividing TGUR by both the plasma glucose (mg/dL) and serum insulin (μU/mL) levels at the end of the clamp and then multiplying the resulting value by 100. In the case of the control group, given that urinary glucose excretion was negligible and that GIR could thus be considered to be equal to TGUR during the clamp, ISI was calculated by dividing the mean GIR during the final 30 min of the clamp by both plasma glucose and serum insulin levels at the end of the clamp.

Metabolic parameters

HOMA-IR was calculated from a blood sample obtained on the day of the glucose clamp in both the SGLT2 inhibitor and control groups according to the formula: [fasting plasma glucose level (mg/dL) × fasting serum insulin level (μU/mL)]/405. Plasma glucose concentration was determined by the glucose oxidase method, and serum insulin level by a double-antibody radioimmunoassay. Data for age, sex, body mass index, diabetes duration, glycated hemoglobin (HbA_{1c}) level, and medications were collected from medical records. Japan Diabetes Society (JDS) values for HbA_{1c} were converted to National Glycohemoglobin Standardization Program (NGSP) values [25].

Statistical analysis

Results are presented as means ± SD for normally distributed data and as the median (interquartile range) for nonnormally distributed data. Intergroup differences of normally or nonnormally distributed data were tested for significance with the unpaired Student's *t* test or Mann-Whitney *U* test, respectively. In the case of categorical data, the chi-square test or Fisher's exact test was applied. Simple linear regression analysis was adopted to assess the relation between HOMA-IR and ISI. Differences in regression lines between the SGLT2 inhibitor and control groups were assessed by analysis of covariance. Multiple regression analysis was applied to build an estimated ISI formula appropriate for both SGLT2 inhibitor and control groups. A p value of <0.05 was considered statistically significant, and all statistical analysis was performed with SPSS ver. 22.0 software (IBM, Armonk, NY).

Results

Propensity score matching identified 17 pairs of patients from the 22 patients in the SGLT2 inhibitor group and 44 patients in the control group. There were no significant differences in diabetes duration, fasting plasma glucose or serum insulin concentrations, or HbA_{1c} level between the two groups (Table 1). With respect to medications, however, there was a significant difference in the number of patients treated with sulfonylureas between the SGLT2 inhibitor group and the control group (0% and 29.4%, respectively, $p = 0.044$) (Table 2). The parameters in the clamp analysis were shown in Table 3. GIR, TGUR, and serum insulin level at steady state were not different in both groups, whereas plasma glucose level of steady state was lower in control group than that in SGLT2 inhibitor group.

A scatter plot revealed a hyperbola-like relation between HOMA-IR and ISI in both the SGLT2 inhibitor and control groups (Fig. 1A). We applied a natural logarithmic transformation to the data for HOMA-IR, which were nonnormally distributed. A significant linear relation was apparent between log-transformed HOMA-IR and ISI in both the SGLT2 inhibitor group ($r = -0.527$, $p = 0.030$) and the control group ($r = -0.534$, $p = 0.027$). These results suggested that HOMA-IR is correlated with ISI in individuals undergoing treatment with an SGLT2 inhibitor as well as in those not receiving such treatment. Simple regression analysis showed that the formulas relating log-transformed HOMA-IR to ISI were as follows: $y = (-1.52 \times 10^{-4})x + (4.50 \times 10^{-4})$, where y is ISI and x is log-transformed HOMA-IR, in the SGLT2 inhibitor group ($p = 0.030$, $R^2 = 0.277$), and $y = (-1.92 \times 10^{-4})x + (6.15 \times 10^{-4})$ in the control group ($p = 0.027$, $R^2 = 0.286$) (Fig. 1B). The slopes of the linear regression lines did not significantly differ between the two groups

Table 1 Clinical characteristics of the paired study participants

Characteristic	SGLT2 inhibitor group ($n = 17$)	Control group ($n = 17$)	p
Age (years)	57.9 ± 9.6	58.0 ± 14.2	0.978
Sex (male/female)	13/4	9/8	0.151
Body mass index (kg/m^2)	25.0 ± 2.5	25.1 ± 4.6	0.812
Diabetes duration (years)	7.0 (0.0–16.5)	6.0 (2.5–13.0)	0.919
Fasting plasma glucose (mg/dL)	98.7 ± 17.6	102.8 ± 19.7	0.525
Fasting serum insulin (μU/mL)	4.0 (3.5–5.8)	6.0 (4.0–8.0)	0.114
HbA_{1c} level (%)	8.2 ± 1.6	8.7 ± 1.8	0.472

Data are presented as means ± SD for normally distributed data, medians (25%–75% range) for nonnormally distributed data, or n values for categorical data. The p values are for comparison between the SGLT2 inhibitor and control groups. Abbreviations: SGLT2, sodium-glucose cotransporter 2; HbA_{1c}, glycated hemoglobin.

Table 2 Medications for the paired study participants

Medication	SGLT2 inhibitor group (n = 17)	Control group (n = 17)	p
Antidiabetic			
Sulfonylurea	0 (0.0)	5 (29.4)	0.044
Glinide	2 (11.8)	1 (5.9)	1.000
Biguanide	16 (94.1)	16 (94.1)	1.000
DPP-4 inhibitor	10 (58.8)	11 (64.7)	0.724
α-Glucosidase inhibitor	4 (23.5)	4 (23.5)	1.000
Short-acting insulin	0 (0.0)	4 (23.5)	0.103
Antihypertensive			
Ca^{2+} channel blocker	4 (23.5)	5 (29.4)	1.000
ACE-I or ARB	7 (41.2)	9 (52.9)	0.492
Diuretic	1 (5.9)	1 (5.9)	1.000
Lipid-lowering			
Statin	5 (29.4)	8 (47.1)	0.481
Fibrate	1 (5.9)	1 (5.9)	1.000
Ezetimibe	1 (5.9)	1 (5.9)	1.000

Data are presented as n (%). Abbreviations: SGLT2, sodium-glucose cotransporter 2; DPP-4, dipeptidyl peptidase-4; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 3 Parameters in clamp analysis

Characteristic	SGLT2 inhibitor group (n = 17)	Control group (n = 17)	p
GIR (mg/kg/min)	5.30 ± 1.38	4.74 ± 1.32	0.238
UGER (mg/kg/min)	1.19 ± 0.46	NA	NA
TGUR (mg/kg/min)	4.54 ± 1.38	4.74 ± 1.32	0.671
Plasma glucose at steady state (mg/dL)	91.6 ± 7.10	81.8 ± 14.8	0.022
Serum insulin at steady state (μU/mL)	114.6 ± 18.0	122.9 ± 25.0	0.272

Data are presented as means ± SD for normally distributed data, medians (25%–75% range) for nonnormally distributed data. The p values are for comparison between the SGLT2 inhibitor and control groups. Abbreviations: SGLT2, sodium-glucose cotransporter 2; GIR, glucose infusion rate; UGER, urinary glucose excretion rate; TGUR, tissue glucose uptake rate; NA, not available.

(p = 0.716), but the intercepts differed significantly (p = 0.002), indicating that HOMA-IR values corresponding to the same ISI were lower in patients treated with the SGLT2 inhibitor than in those not receiving this medication.

To obtain a regression formula for prediction of ISI in both the SGLT2 inhibitor group and the control group, we applied multiple regression analysis in which the absence or presence of SGLT2 inhibitor treatment was considered an independent variable together with log-transformed HOMA-IR. The resulting formula was as follows: $y = (6.10 \times 10^{-4}) - (1.78 \times 10^{-4})x - (1.59 \times 10^{-4})z$, where y is ISI, x is log-transformed HOMA-IR, and z is 1 in the SGLT2 inhibitor group and 0 in the control group (p = 0.018, R^2 = 0.327). In addition, multivariate analysis yielded a formula for comparison of HOMA-IR between patients with the same ISI in the SGLT2 inhibitor ($SGLT2_i$) and control groups: $HOMA\text{-}IR_{control} = HOMA\text{-}IR_{SGLT\text{-}2i} \times 2.45$.

Discussion

Whereas SGLT2 inhibitors reduce blood glucose levels by promoting urinary glucose output, these drugs also appear to induce various humoral and metabolic changes that may affect insulin resistance-sensitivity [17-22]. We therefore investigated whether HOMA-IR, a widely adopted marker for insulin resistance-sensitivity, actually reflects this parameter during treatment with an SGLT2 inhibitor.

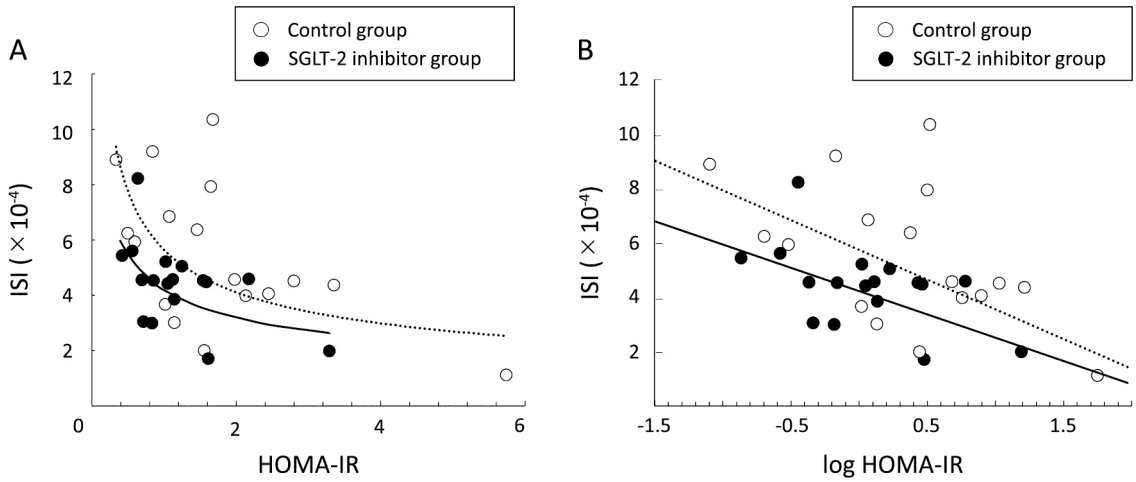

Fig. 1 Relation between HOMA-IR and ISI in 17 pairs of type 2 diabetic subjects in the SGLT2 inhibitor and control groups
ISI was plotted against HOMA-IR (A) or natural log–transformed HOMA-IR (B) for both the SGLT2 inhibitor and control groups. Regression lines are shown (solid line, SGLT2 inhibitor group; dotted line, control group).

We found that the correlation between HOMA-IR and clamp-derived ISI was well conserved in the SGLT2 inhibitor group compared with the control group, indicating that HOMA-IR is a suitable marker of insulin resistance-sensitivity in individuals treated with SGLT2 inhibitors. However, the absolute value of HOMA-IR corresponding to the same ISI was smaller in the SGLT2 inhibitor group than in the control group. The relation between HOMA-IR values in the two groups was expressed by the formula: $\text{HOMA-IR}_{\text{control}} = \text{HOMA-IR}_{\text{SGLT2i}} \times 2.45$. As far as we are aware, our study is the first to characterize the relation between HOMA-IR and clamp-derived ISI in patients treated with an SGLT2 inhibitor.

Log-transformed HOMA-IR was previously shown to be well correlated with a clamp-derived insulin sensitivity index in subjects treated with sulfonylureas and in those treated with diet modification alone, with both the slopes and intercepts in regression analysis being similar between the two groups [26], indicating that the value of HOMA-IR should theoretically be the same for individuals with the same ISI regardless of whether they are receiving treatment with sulfonylureas or not. We have now found that, whereas the slopes were similar, the intercept of regression analysis for log-transformed HOMA-IR and ISI was smaller for patients in the SGLT2 inhibitor group than for those in the control group, indicating that the value of HOMA-IR corresponding to the same ISI is smaller if patients are treated with an SGLT2 inhibitor. Given that SGLT2 inhibitors promote the excretion of glucose from blood to urine, a smaller amount of circulating insulin is likely required to maintain glycemia at a certain level in patients receiving than in those not receiving such drugs if they possess the same level of insulin sensitivity, with the result that HOMA-IR is smaller in the former individuals. Given that hyperinsulinemia is associated with an increased risk of various conditions [27-29], such a smaller insulin requirement for maintenance of glycemia may be related to the beneficial clinical features of SGLT2 inhibitors.

The number of subjects treated with sulfonylureas in the present study differed between the SGLT2 inhibitor and control groups. However, sulfonylureas did not affect the relation between HOMA-IR and insulin sensitivity determined by clamp analysis [26], so this difference is likely to have had little effect on our results. Given that urinary glucose excretion is usually negligible during euglycemia, TGUR is effectively equal to GIR during hyperinsulinemic-euglycemic clamp analysis. However, GIR does not reflect TGUR in individuals treated with SGLT2 inhibitors, given that these drugs increase urinary glucose excretion even during the euglycemic condition [30]. We therefore measured urinary glucose excretion and calculated ISI with the use of TGUR (GIR adjusted for urinary glucose excretion) in subjects of the SGLT2 inhibitor group.

Limitations of the present study include its one-arm design. In addition, we did not evaluate HOMA-IR and ISI in the same patients before and after treatment with an SGLT2 inhibitor, but instead used a different cohort as a control for SGLT2 inhibitor treatment. However, we did perform propensity score matching in order to minimize deviation due to differences between the two groups. The number of subjects in the present study is also relatively small, with the result that a study with a larger number of subjects will be required to confirm our findings.

In conclusion, we found that, whereas HOMA-IR is

well correlated with ISI in patients treated with an SGLT2 inhibitor, its absolute value corresponding to the same ISI is smaller in these individuals than in those not receiving such treatment. Health care providers as well as clinical investigators should thus keep this difference in mind when they measure and analyze HOMA-IR in patients treated with SGLT2 inhibitors. The simple transformation formula, $\text{HOMA-IR}_{\text{control}} = \text{HOMA-IR}_{\text{SGLT2i}} \times 2.45$, should prove helpful for interpretation of HOMA-IR values in patients treated with an SGLT2 inhibitor.

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Disclosure

Author contributions

AS, KS, YO and WO conceived and designed the study. AS, YM, TY, HM, NO-S, HK and YH contributed to the collection of date. AS, KS and YT analysed and interpreted the date. AS, KS and YT wrote the paper. WO contributed to the writing of the manuscript. All authors contributed to discussion, reviewed the manuscript critically for important intellectual contact and approved the final version to be published. KS is responsible for the integrity of the work as a whole.

Conflicts of interest

KS has received research support from AstraZeneca and Ono Pharmaceutical Co. Ltd. All other authors declare no potential conflicts of interest.

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