Research: Treatment

Influence of an SGLT2 inhibitor, tofogliflozin, on the resting heart rate in relation to adipose tissue insulin resistance

T. Nojima1,2, Y. Matsubayashi1, A. Yoshida1,3, H. Suganami2, T. Abe1, M. Ishizawa1, K. Fujihara1, S. Tanaka4, K. Kaku5 and H. Sone1

1Department of Hematology, Endocrinology and Metabolism, Niigata University Faculty of Medicine, Niigata, 2Clinical Data Science Department, 3Kowa Co., Ltd., Tokyo, Japan, 4Department of Clinical Biostatistics, Graduate School of Medicine, Kyoto University, Kyoto and 5Kawasaki Medical School, Okayama, Japan

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Abstract

Aims To examine the effects of a sodium–glucose co-transporter 2 (SGLT2) inhibitor, tofogliflozin, on resting heart rate by exploring baseline factors that independently influenced changes in the resting heart rate.

Methods Data on 419 participants in tofogliflozin phase 2/3 trials were analysed. Changes in resting heart rate from baseline to week 24 were analysed using an analysis of covariance (ANCOVA) model with groups (tofogliflozin/placebo) as a fixed effect and baseline values as covariates. The antilipolytic effect was evaluated as adipose tissue insulin resistance (Adipo-IR) and was calculated as the product of fasting insulin and free fatty acid. Multivariate analysis evaluated independent factors for changes in resting heart rate from baseline to week 24.

Results Of the participants, 58% were men, and mean age, HbA1c, BMI and resting heart rate were 57.6 years, 65 mmol/mol (8.1%), 25.5 kg/m² and 66 bpm, respectively. At week 24, adjusted mean difference vs. placebo in the change from baseline was 2.3 bpm [95% confidence interval (CI) −4.6, 0.1] with tofogliflozin. Changes in resting heart rate were positively correlated with changes in Adipo-IR, whereas reductions in HbA1c, body weight and blood pressure were similar independent of changes in resting heart among quartiles of resting heart rate change. On multivariate analysis, higher baseline resting heart rates and Adipo-IR values were significantly associated with greater reductions in resting heart rate.

Conclusions Tofogliflozin corrected resting heart rate levels in accordance with baseline levels. Correction of high resting heart rates may be attributed to improved adipose tissue insulin resistance, leading to correction of hyperinsulinemia.

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Introduction

Resting heart rate is determined by the activity of the sinoatrial node. It is considered a marker of autonomic nervous system activity and is largely influenced by the interaction of sympathetic and vagal activities [1]; thus an elevated resting heart rate implies sympathetic hyperactivity and/or reduced parasympathetic activity [2]. Epidemiological evidence from the general population suggests that a high resting heart rate is related to increased cardiovascular morbidity and mortality independent of conventional risk factors [3]. Furthermore, in the ADVANCE study of type 2 diabetes mellitus, a high resting heart rate was reported as a risk factor for not only cardiovascular disease, but also microvascular complications [4,5]. Insulin resistance and elevated sympathetic system activity were reported to be closely related [6,7].

A sodium–glucose co-transporter 2 (SGLT2) inhibitor facilitates urinary glucose excretion by inhibiting SGLT2 in the proximal tubule and produces weight loss, in particular, reduction in fat mass, as well as a reduction in blood glucose [8]. In addition, as it lowers the blood glucose level without promoting insulin secretion, it has been reported to decrease fasting and postprandial insulin levels, and improve insulin...
What’s new?

- A high resting heart rate is related to increased cardiovascular and microvascular risks in persons with type 2 diabetes.
- Tofogliflozin significantly reduced resting heart rate compared with placebo, irrespective of reductions in HbA1c, body weight and blood pressure.
- Reduction in resting heart rate was associated with improvements in adipose tissue insulin resistance.
- Higher baseline adipose tissue insulin resistance levels were independently associated with a greater decline in resting heart rate.
- Correcting the resting heart rate via improved adipose tissue insulin resistance by tofogliflozin treatment might contribute to lowering the risks of cardiovascular diseases.

Participants and methods

We conducted a pooled analysis of data from two tofogliflozin phase 2/3 trials that followed participants with type 2 diabetes for at least 24 weeks (Table 1). CSG003JP (placebo; tofogliflozin 10, 20 and 40 mg monotherapy) was a 24-week multicentre, randomized, placebo-controlled, double-blind, phase 2/3 trial [14]. CSG004JP (tofogliflozin 20 and 40 mg monotherapy) was a 52-week, multicentre, randomized, controlled, open-label phase 3 trial [15]. Major inclusion criteria were: (1) participants aged at least 20 years old (CSG003JP) or 20–74 years old (CSG004JP) with type 2 diabetes; (2) BMI of 18.5–44.9 kg/m²; and (3) HbA1c at screening of ≥ 51 mmol/mol (6.8%) (CSG003JP) or ≥ 56 mmol/mol (7.3%) (CSG004JP) to < 89 mmol/mol (10.3%). Details of the design and results of the above...
studies, including inclusion and exclusion criteria, have been reported previously [14,15]. Data acquired from baseline, that is, from week 0 of study entry, to week 24 of each study were included in this pooled analysis. All studies were conducted in accordance with the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines. The protocol was reviewed and approved by the Institutional Review Committee of each participating centre. Before enrolment into the two trials, all participants had provided written informed consent, including permission to use the resultant data. These trials were registered by the Japan Pharmaceutical Information Center clinical trials information (JapicCTI) as 101349 and 101351.

Measurements

The following baseline laboratory values were used: HbA1c, fasting plasma glucose, fasting insulin, fasting C-peptide, fasting free fatty acids, homeostatic model assessment of insulin resistance scores [HOMA-IR: F-IRI (μU/ml × fasting plasma glucose (mg/dl)/405)], 24-variable homeostasis model assessment of β-cell function (iHOMA2%β) and insulin sensitivity (iHOMA2%S) [16], and Adipo-IR determined by fasting insulin × fasting free fatty acid [17], which was reported to be associated with insulin sensitivity in adipose tissue using the clamp method [18]. Values for adiponectin, uric acid, haematocrit, serum creatinine and the eGFR calculated from serum creatinine [19] were determined. Furthermore, assessments using study baseline data included BMI, waist circumference, SBP, DBP, mean average pressure [DBP + (SBP – DBP)/3], pulse pressure (SBP – DBP), double product (SBP × resting heart rate) and pulse rate. A meal tolerance test was performed in the CSG004JP study. For that study, after fasting for at least 10 h, participants came to the medical institution taking part in the clinical trials and underwent a meal tolerance test. The test meal contained 314 kcal (1314 kJ; 5.45 g protein, 73.05 g carbohydrate and 0 g lipids). Urinary glucose excretion during the meal tolerance test was measured.

Statistical analysis

In each group, the demographics were summarized with appropriate descriptive statistics (means and SD for continuous variables, and frequencies and percentages for categorical variables). In addition, differences in baseline assessments across groups were analysed using Student’s t-test and Fisher’s exact test. Assessments of changes in the resting heart rate from baseline to week 24 were analysed using an analysis of covariance (ANCOVA) model with the group as a fixed effect and baseline values as covariates to determine differences across groups. The amount of change was calculated for each participant from the values at two time points, baseline (week 0) and 24 weeks after administration as an endpoint. Also, as an exploratory analysis, the change in resting heart rate from baseline to week 24 was compared between participants who did and did not use a concomitant anti-hypertensive agent (angiotensin II receptor blocker, angiotensin converting enzyme inhibitor, calcium channel blocker, β-blocker and diuretic); for this analysis, an ANCOVA model was used with the anti-hypertensive agent as the fixed effect and baseline values as covariates to examine differences between using and not using such an agent. Analyses of the correlation or relationship between resting heart rate and other variables were performed using Pearson’s product-moment correlation coefficients and Spearman rank-order correlation coefficients. Participants receiving tofogliflozin were divided into four groups based on quartiles of change in resting heart rate from baseline to week 24. Laboratory variables were also evaluated from baseline to week 24.

Multivariate general linear models were fitted to the change in resting heart rate from baseline to week 24. Covariates in the models included: sex; age; angiotensin II receptor blocker, angiotensin converting enzyme inhibitor, calcium channel blocker, β-blocker and diuretic dosages; duration of diabetes; DBP; HbA1c; fasting plasma glucose level; BMI; haematocrit; eGFR; uric acid level; Adipo-IR; HOMA-IR; iHOMA2%S; iHOMA2%β; adiponectin level; and resting heart rate at baseline. The variables in the models were selected through stepwise variable selection with P < 0.05. Resting heart rate was measured using a 12-lead ECG. Data were analysed using the SAS system, Release 9.3 (SAS Institute, Cary, NC, USA). The significance level for each test was 0.05 (two-sided).

Results

Data collected at baseline and week 24 of tofogliflozin or placebo administration were examined in people with type 2 diabetes who had insufficient glycaemic control using diet and exercise therapy (placebo: n = 56; tofogliflozin: n = 363) (Table 1). The average age of the target population was 57.6 years and BMI was 25.5 kg/m², HbA1c was 65 mmol/mol (8.1%), and resting heart rate was 66 bpm. At week 24, the change in resting heart rate was −1.1 bpm in the tofogliflozin group and +1.2 bpm in the placebo group; the decrease in the tofogliflozin group was significant in comparison with that in the placebo group, as indicated by ANCOVA (P = 0.041). In the tofogliflozin group, a negative correlation was observed between the change in resting heart rate and the baseline value, with a greater resting heart rate reduction at week 24 in participants with higher baseline values (r = −0.37) (Fig. 1). Baseline resting heart rate values were the same in the placebo group as in the tofogliflozin group.

Associations of changes in resting heart rate with other variables after tofogliflozin administration

Baseline factors were compared among participants divided according to quartiles of resting heart rate change after tofogliflozin administration (Table 2). HOMA-IR and Adipo-
IR, which are indicators of insulin resistance, were highest, and iHOMA2%S, which is an index of insulin sensitivity, was the lowest in the Quartile 1 (Q1) group. The greatest reduction in resting heart rate (least squares mean -11.2 bpm) among quartiles was observed in Q1 (Fig. 2). Changes in each variable from baseline were examined according to quartiles of resting heart rate change after tofogliflozin administration (Table 3). For each change in SBP, DBP, HbA1c and body weight, the same degree of decrease was observed among quartiles of the resting heart rate change (Fig. 2). Among glucose-related indicators, fasting plasma glucose, C-peptide and postprandial blood glucose area under the curve (AUC0-120min) had the greatest decreases in Q1 as did Adipo-IR and insulin, which are indicators of insulin resistance. A significant positive correlation was also observed between the reduction in resting heart rate and Adipo-IR levels (Fig. 1).

Baseline predictors that influenced changes in resting heart rate

Baseline factors that affected changes in resting heart rate were examined by multivariate analysis (Table 4). Higher baseline resting heart rate and Adipo-IR values were significantly associated with a greater decline in resting heart rate (for each 1 unit increase, declines were 0.24 and 0.07, respectively), whereas higher baseline iHOMA2%β and eGFR were significantly associated with an increase in resting heart rate. Even when these factors were adjusted, tofogliflozin significantly reduced the resting heart rate compared with placebo.

Discussion

This study is the first to evaluate the influence of an SGLT2 inhibitor on resting heart rate and factors related to such an influence. The SGLT2 inhibitor, tofogliflozin, was shown to significantly reduce resting heart rate compared with a placebo. Furthermore, an ~11 bpm reduction in resting heart rate was observed in participants with higher baseline resting heart rate and greater insulin resistance. This decrease was also associated with improvements in adipose tissue insulin resistance. Therefore, it was speculated that the correction in resting heart rate was associated with normalization of sympathetic nervous activity by not only correcting hyperglycaemia, but also improving adipose tissue insulin resistance, leading to the correction of hyperinsulinaemia.

Epidemiological studies have shown that a high heart rate is an independent risk factor for cardiovascular disease or death [20]. It was reported that an elevated resting heart rate presents a risk of cardiovascular disease and microvascular disease in type 2 diabetes [4,5]. In the current study, the resting heart rate showed a significant decrease at week 24 in the tofogliflozin group compared with the placebo group. In particular, a negative correlation was found between the change in resting heart rate from baseline to week 24 and the baseline resting heart rate; participants with a high baseline resting heart rate had a greater decrease in resting heart rate. Therefore, we infer that tofogliflozin effectively corrects high resting heart rate values. Interestingly, irrespective of the change in resting heart rate, the same degree of reduction in HbA1c, body weight and blood pressure was observed among the quartiles of resting heart rate change. Previous reports have suggested that SGLT2 inhibitors lead to a reduction in blood pressure without affecting heart rate [21,22]. That the degree of blood pressure reduction was not significantly different in this study among groups according to quartiles of resting heart rate, that is, irrespective of heart rate change, is consistent with these past reports. Taken together, these results suggest that SGLT2 inhibitors affect the resting heart
higher baseline Adipo-IR levels were significantly associated with a high resting heart rate [6]. However, this is the first study to show the relationship between insulin resistance and resting heart rate. In the current study, baseline resting heart rate levels were positively correlated with baseline indices of insulin resistance.

In this investigation, a significant correlation between resting heart rate reduction and Adipo-IR change was recognized. Results of multivariate analysis suggested that higher baseline Adipo-IR levels were significantly associated with greater declines in resting heart rate. Previously, the relationship between insulin resistance and resting heart rate was examined and strong insulin resistance was found to be associated with a high resting heart rate [6]. However, this is the first study to show the relationship between insulin resistance in adipose tissue and resting heart rate. In the current study, baseline resting heart rate levels were positively correlated with baseline indices of insulin resistance.
all study participants (Table 5). SGLT2 inhibitors reduced body weight as both monotherapy and add-on therapy [14,15,23]. It was reported that about two-thirds of body weight loss was caused by a decrease in fat mass and one-third was caused by a decrease in lean body mass, which suggests that a reduction in fat mass is the main cause of the weight loss [24,25]. Although body composition was not measured in this study, on the basis of these previous findings, it can be speculated that SGLT2 inhibitors improve insulin resistance, particularly in adipose tissue, by inducing weight loss. Results of a study of the relationship between insulin resistance (hyperinsulinaemia) and sympathetic hyperactivity [6] indicated that tofogliflozin might suppress sympathetic hyperactivity via improvement in adipose tissue insulin resistance. Furthermore, a decrease in heat production by adipocytes following reductions in resting heart rate has been reported [26]. Therefore, it may be possible to lower the resting heart rate by fat reduction through administering a SGLT2 inhibitor (adipose tissue insulin resistance improvement), thereby decreasing heat production and maintaining energy homeostasis. In addition, SGLT2 inhibitors have been reported to have anti-inflammatory effects in clinical situations [27,28]. Experimentally, SGLT2 inhibitors were reported to improve baroreceptor reflex sensitivity [29]. In particular, Yoshikawa et al. [29] showed that the heart rate is optimized during the active period (sympathetic dominant) and is not affected during the inactive period (parasympathetic dominant). There is a possibility that anti-inflammatory activity and sympathetic nerve activity are related. In this study, Adipo-IR, that is, insulin resistance in adipose tissue, was evaluated as the product of fasting insulin and free fatty acids. Henceforth, it will be necessary to accurately, that is, directly, evaluate adipose tissue insulin resistance by the glucose clamp method or similar methods, and evaluate the relationship between adipose tissue insulin resistance and the heart rate or sympathetic nerve activity.

The EMPA-REG OUTCOME study also suggested a reduction in resting heart rate [10]. An improvement in the prognosis of cardiovascular disease following a reduction in heart rate by drug interventions was reported [3]. This was supported by interventional studies reporting that reductions in heart rate through correction of sympathetic nervous system activity were related to an improved prognosis [30]. The results of the current investigation indicated that SGLT2 inhibitors may reduce resting heart rate in individuals with

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**FIGURE 2** Changes in resting heart rate and other parameters from baseline at week 24 in study participants administered tofogliflozin: (a) resting heart rate, (b) HbA1c, (c) body weight and (d) blood pressure (■, SBP; □, DBP). Participants were divided into four groups according to quartiles of change in resting heart rate at week 24. Data are expressed as least squares mean (±SE). Analyses are performed by ANCOVA (Covariate: Baseline) to test across the groups. ***P < 0.001 t-test for least squares mean.
Table 3 Changes in variables according to quartiles of change in resting heart rate at week 24 after administration of tofogliflozin

| Quartile 1 (Δ resting heart rate < −5) | Quartile 2 (−5 ≤ Δ resting heart rate < −1) | Quartile 3 (−1 ≤ Δ resting heart rate < 0) | Quartile 4 (4 ≤ Δ resting heart rate) | P-value |
|--------------------------------------|---------------------------------------------|-------------------------------------------|--------------------------------------|---------|
| (n = 76)                             | (n = 84)                                     | (n = 92)                                   | (n = 92)                             |         |
| eGFR (ml min \(^{-1}\) 1.73m\(^{-2}\)) | −0.2 (1.0)                                  | 0.3 (0.9)                                 | −0.2 (0.9)                           | 0.741   |
| Waist circumference (cm)             | −3.0 (0.4)***                               | −2.4 (0.4)***                             | −2.2 (0.4)***                        | 0.486   |
| BMI (kg/m\(^2\))                    | −1.2 (0.1)***                               | −1.1 (0.1)***                             | −1.1 (0.1)***                        | 0.519   |
| Fasting plasma glucose (mmol/l)      | −2.1 (0.1)***                               | −1.9 (0.1)***                             | −1.7 (0.1)***                        | 0.037   |
| Fasting insulin (pmol/l)             | −17.3 (1.8)**                               | −16.2 (1.7)**                             | −14.0 (1.6)**                        | 0.003   |
| Fasting C-peptide (pmol/l)           | −79.7 (13.2)**                               | −67.6 (12.4)**                            | −53.8 (11.8)**                       | 0.032   |
| Glucose AUC\(_{0-120min}\) (mmol/l) | −6.8 (0.3)**†                               | −5.9 (0.3)**†                             | −5.9 (0.3)**†                        | 0.017   |
| Insulin AUC\(_{0-120min}\) (pmol/l) | −49.2 (11.8)**                               | −53.3 (11.0)**                            | −68.1 (10.6)**                       | 0.607   |
| C-peptide AUC\(_{0-120min}\) (pmol/l) | 3.3 (0.4)**                                 | 3.5 (0.4)***)                             | 3.5 (0.4)***)                        |         |
| Adipo-IR (µg/mL)                     | 9.2 (1.5)**†                                | 6.4 (1.4)***)                             | 5.5 (1.4)***)                        | 0.320   |
| Fasting free fatty acid (mmol/l)     | 0.05 (0.03)                                 | 0.07 (0.02)**                             | 0.09 (0.02)**                        | 0.108   |
| Adipo-IR (µmol·pmol\(^{-1}\))       | −12.6 (1.9)**†                              | −5.4 (1.8)***)                            | −2.8 (1.7)**                         | <0.001  |
| Adiponectin (µg/mL)                  | 0.8 (0.2)**†                                | 0.8 (0.2)***)                             | 0.5 (0.2)**                         | 0.416   |
| Uric acid (mg/dL)                    | −0.4 (0.1)**†                               | −0.5 (0.1)***)                            | −0.4 (0.1)**                         | 0.161   |
| Hematocrit (%)                       | 0.4 (0.3)                                   | 0.6 (0.2)***)                             | 0.6 (0.2)**                         | 0.338   |
| Urinary albumin to creatinine ratio  | −71.5 (32.2)***                            | −57.7 (30.4)**                            | −49.8 (29.1)**                      | 0.094   |
| (µmol/mmol Cr)                       |                                             |                                             |                                     |         |
| Mean average pressure (mmHg)         | −5.1 (0.9)**†                               | −6.5 (0.9)***)                            | −6.2 (0.9)**                         | 0.574   |
| Pulse pressure (mmHg)                | −2.6 (1.1)**†                               | −2.7 (1.0)***)                            | −2.8 (1.0)**                         | 0.578   |
| Double product\(_{0-120min}\)       | −1786.7 (118.8)**                           | −1000.2 (108.1)**                        | −460.6 (103.6)**                    | <0.001  |
| Pulse rate (high)                    | −6.0 (0.8)**†                               | −2.1 (0.8)***)                            | 0.3 (0.7)**                         | <0.001  |
| (higher 1 bpm)                       |                                             |                                             |                                     |         |

Data are expressed as least square mean (st). Analyses are performed by ANCOVA (covariate: baseline) to test across the groups.

\*P < 0.05, \**P < 0.01, \***P < 0.001; t-test for least squares mean.
†From the iHOMA2 model.
‡Fasting insulin (pmol/l)-fasting free fatty acid (mmol/l).
§DBP = SBP − DBP/3.

Table 4 Baseline predictors that influenced the change in resting heart rate at week 24

| Factor                                          | Regression coefficient | P-value |
|-------------------------------------------------|------------------------|---------|
| iHOMA2beta (higher 1 unit)                      | 0.06                   | 0.020   |
| eGFR (ml min \(^{-1}\) 1.73m\(^{-2}\)) (higher 1 ml mm\(^{-1}\) 1.73m\(^{-2}\)) | 0.07                   | 0.001   |
| Resting heart rate (bpm) (higher 1 bpm)         | −0.07                  | 0.002   |
| Tofogliflozin (vs. placebo)                     | −2.35                  | 0.048   |

Factors remained through stepwise variable selection with P < 0.05.

Potential baseline predictors were tofogliflozin (vs. placebo), angiotensin II receptor blocker (use vs. nonuse), angiotensin converting enzyme inhibitor (use vs. nonuse), calcium channel blocker (use vs. nonuse), β-blocker (use vs. nonuse), diuretics (use vs. nonuse), age, sex, duration of diabetes, DBP, HbA1c, fasting plasma glucose, BMI, hematomctric, eGFR, uric acid, Adipo-IR, HOMA-IR, iHOMA2S, iHOMA2B, adiponectin and resting heart rate.

disease. Participants in the current study were individuals with type 2 diabetes who were enrolled in phase 2/3 studies that compared tofogliflozin with placebo, and who had previously been treated by diet and exercise only. In an actual clinical setting, some concomitant therapies, including anti-hyperglycaemia and anti-hypertensive treatments, are needed to control cardiovascular risk factors in people with type 2 diabetes. An increase in resting heart rate has been reported for glucagon-like peptide 1 (GLP-1) receptor agonists that resulted in weight loss, unlike SGLT2 inhibitors [31]. It can be speculated that elevation in the resting heart rate caused by GLP-1 receptor agonists is the result of stimulation of the GLP-1 receptor in the sinoatrial node. Thus, it is quite interesting that the influence on resting heart rate differs between drugs producing similar reductions in blood glucose, weight and cardiovascular composite events. In our exploratory analysis (Table 6), a greater reduction in resting heart rate was observed in participants administered a concomitant β-blocker than in those without that agent, although the effect of concomitant anti-hypertensive drugs was not observed in the multivariate analysis. We could not clarify the effect of concomitant anti-hypertensive agents on resting heart rate because the number of participants using concomitant anti-hypertensive agents was so small. Therefore,
This study has several limitations that must be considered. It was not a prospective study; therefore, a long-term prospective study remains necessary. The number of participants was not sufficient to consider the effects of anti-hypertensive agents in both the placebo and tofogliflozin groups, nor were humoral factors affecting sympathetic and parasympathetic nervous activity measured. Fluctuations in the heart rate were not observed using 24-h Holter monitoring in any of the participants. In the future, it will also be necessary to evaluate adipose tissue insulin resistance using the glucose clamp or a similar method. Body composition and inflammatory markers were not measured. The relationship between weight loss and adipocytes, and the relationship between proinflammatory cytokines and sympathetic overactivity should be investigated in the future. Furthermore, because none of the participants in the present study had heart disease, individuals with heart disease and a long duration of diabetes must be studied.

The SGLT2 inhibitor tofogliflozin corrected resting heart rate levels in accordance with baseline levels. The correction of high resting heart rates may be attributed to the improvement of adipose tissue insulin resistance, leading to the correction of hyperinsulinaemia.
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Author contributions

T.N., Y.M. and H.So. contributed to the conception and design of this study. T.N. contributed to interpretation of data, writing of the first draft and revision of the manuscript for important intellectual content. H.So. contributed to the interpretation of the data and revised the manuscript for important intellectual content. H.Su., T.N. and S.T. contributed to the design of this study. T.N. contributed to interpretation of the data, writing of the first draft and revision of the manuscript for important intellectual content. H.So., T.N., Y.M. and H.So. contributed to the conception and design of this study. T.N., Y.M. and H.So. contributed to the conception and design of this study. T.N., Y.M. and H.So.

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