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Effects of dapagliflozin compared with glimepiride on body composition in Asian patients with type 2 diabetes inadequately controlled with metformin: The BEYOND study

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Abstract

Aims: To evaluate the effect of dapagliflozin on body composition such as total body fat (BF) mass, abdominal visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) areas compared with glimepiride in Korean patients with type 2 diabetes.

Materials and Methods: This was a 52-week, multicentre, randomized, parallel-group, open-label, Phase IV (NCT02564926) study. Patients with inadequate glycaemic control (glycated haemoglobin ≥7.0% and <10.0%) on metformin monotherapy (≥1000 mg/day) were randomized 1:1 to receive dapagliflozin 10 mg/day or glimepiride 1-2 mg/day for 12 months as an add-on to metformin. Baseline and end of study

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body composition evaluations included dual-energy X-ray absorptiometry and abdominal computed tomography scans.

Results: Of 124 enrolled patients from 14 centres, 121 received study treatment (dapagliflozin: 60; glimepiride: 61) and 106 (85.5%) completed the study. Over 52 weeks, the dapagliflozin group showed the following differences versus the glimepiride group: −2.59 kg BF mass, −1.94% BF%, −17.55 cm^2 VAT area, −18.39 cm^2 SAT area, −0.46% glycated haemoglobin, −18.25 mg/dl fasting blood glucose, −3.7 kg weight, −2.21 cm waist circumference, −1.37 kg/m^2 body mass index, −6.81 mmHg systolic blood pressure and +657.71 ng/ml in adiponectin; all were statistically significant. Both groups had similar incidences of adverse events; however, hypoglycaemic events were mainly (12 of 15) reported in the glimepiride group.

Conclusion: Dapagliflozin reduced total BF mass, abdominal VAT and SAT areas, and showed better glycaemic control than glimepiride. Being safe and well-tolerated, dapagliflozin appears to be a more favourable alternative to sulphonylureas as add-on therapy after metformin monotherapy failure in Korean patients with type 2 diabetes.

KEYWORDS
dapagliflozin, SGLT2 inhibitor, sulphonylureas, type 2 diabetes

1 | INTRODUCTION

Maintenance of optimal body weight is an integral element driving the management of type 2 diabetes (T2D). Empirical evidence from real-world studies have elucidated the association between T2D and the facets of body composition such as total body fat (BF) mass and BF percentage (BF%).[1–3] BF and adiposity play a crucial role in the causal pathway for T2D, alternatively, the disease process may also alter body composition. In addition to glycaemia, increased BF may also have a deleterious impact on diabetes complications.[4]

After failure of first-line metformin monotherapy, additional antidiabetic agent(s) are generally added for glycaemic control.[5,6] International treatment guidelines recommend stepwise intensification of therapy,[5,6] and sulphonylureas (SUs) such as glimepiride, glipizide and gliclazide can be added to metformin as second-line treatment.[7,8] Although, SUs are frequently associated with the adverse effects of weight gain and hypoglycaemia[9] many modern SUs, such as glimepiride, are associated with better safety profiles.[10]

Dapagliflozin, a sodium-glucose cotransporter-2 inhibitor (SGLT-2i), targeting the pathophysiological increase in renal glucose reabsorption, showed promising glucose-lowering effects, and more favourable pleiotropic effects on the risk of composite cardiovascular and renal outcomes.[11,12] Dapagliflozin has also been shown to aid in weight management, a desirable extra-glycaemic goal in diabetes therapy. The increased urinary glucose excretion leads to reduced BF secondary to caloric loss, eventually resulting in short- and long-term weight loss, either as monotherapy, or in combination.[13–16] A study among White patients with T2D with an average body mass index (BMI) of 32 kg/m^2, showed significant reductions in dapagliflozin-treated patients for weight by −2.08 kg, waist circumference by −1.52 cm and BF mass by −1.48 kg, as compared with placebo at 24 weeks.[17] Moreover, dapagliflozin significantly decreased both abdominal visceral adipose tissue (VAT, −258.4 cm^3) and subcutaneous adipose tissue (SAT, −184.9 cm^3) areas, as measured by abdominal magnetic resonance.[17]

Studies on the effects of dapagliflozin on body composition in an Asian population are sparse. Interestingly, data from the Korea National Health and Nutrition Examination Survey 2013-2016 revealed that about half of patients with T2D were non-obese (obesity defined as BMI ≥25.0 kg/m^2).[18] Despite having a lower BMI, East Asians have a greater amount of BF and a tendency to visceral adiposity.[19] On the other hand, current evidence suggests that Asians have lower insulin secretion capacity, which may increase the risk of developing T2D.[20,21] For these reasons, a modern SU, glimepiride, which stimulates insulin secretion, is one of the most commonly used second-line treatments for T2D in Korea[22] and Southeast Asia. It is assumed that the effects of dapagliflozin and glimepiride on body composition are different. In this study, we investigated the effects of dapagliflozin and glimepiride on body composition through changes in total BF mass and total BF% in Korean patients with T2D who were not sufficiently controlled by metformin. We also evaluated effects on abdominal adipose tissue areas and total lean body mass, assessed by changes in abdominal VAT and SAT areas using a computed tomography (CT) scan and change in lean body mass using a dual-energy X-ray absorptiometry (DXA) scan.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a 52-week, multicentre, randomized, parallel-group, open-label, Phase IV (NCT02564926, clinicaltrials.gov) study conducted across 14 centres in Korea between January 2016 and January 2018. The study complied with the Declaration of Helsinki and was consistent with the International Council for Harmonization/Good Clinical Practice Guidelines. The Institutional Review Board of all the participating centres approved this study. All patients gave written informed consent before their study participation. Post baseline patients were evaluated at weeks (±7 days) 4, 12, 24, 36 and 52.

2.2 | Study population, treatment allocation and assessments

Adults aged 19-75 years with T2D and inadequately controlled glycated haemoglobin (HbA1c) of 7.0 to <10.0% on stable metformin monotherapy (≥1000 mg/day) for at least 8 weeks before randomization, were enrolled in the study. Overweight and obesity were defined in accordance with the Asian definition[23,24] as a BMI of 23-24.9 kg/m^2 and ≥25 kg/m^2 respectively. The study eligibility criteria are detailed in Figure S1. Patients were randomly assigned in a 1:1 ratio (block size of 4) by computer-generated random sequence to receive either dapagliflozin (10 mg orally, once daily) or glimepiride (1 mg orally, 1 or 2 tablets at a dose of 1-2 mg/day) as add-on to metformin ≥1000 mg. After clinical evaluation by the investigator, glimepiride was either up-titrated to 2 mg to maintain glycaemic control or down-titrated at any time to prevent hypoglycaemia. Patients received education for healthy lifestyle management as part of their routine diabetes care.

Randomized subjects with lack of glycaemic control during treatment period were prescribed open-label, rescue therapy and these subjects remained in the trial. In case of subjects who were taking glimepiride, an increase of dose to 2 mg preceded first for glycaemic control. If lack of glycaemic control persisted, rescue therapy with any marketed sitagliptinin in a dosage approved in Korea was prescribed. No other rescue therapy was allowed. Patients meeting the following criteria were considered for rescue medication: weeks 4-8, fasting blood glucose (FBG) >240 mg/dl; weeks 8-24, FBG >200 mg/dl; and weeks 24-56, HbA1c >8%. In case of continuing hypoglycaemic events not controlled with glimepiride dose down-titration, patients were permanently withdrawn from the study.

A detailed patient diary collected data of each hypoglycaemic event, including start and stop date and time, related symptoms, plasma glucose value at the time of the event if recorded, intensity of event, contributing factors, medications taken, time of last study drug administration and time of last meal. In case of a major hypoglycaemic event, or more than one minor event since the last visit, the subject was instructed to contact the investigator. Detailed study procedures including physical examination, laboratory investigations and body composition assessments (DXA and abdominal CT scans) at baseline and week 52 are shown in Figure S1. Whole-body DXA estimated body composition is based on the principle that the relative attenuation of two different X-ray energies by body tissues produces a three-component model comprising of total BF mass and lean mass. CT scans evaluated abdominal VAT and SAT areas (Table S1).

2.3 | Study endpoints

The primary efficacy endpoint was the change in total BF mass (assessed using DXA scan) from baseline to 52 weeks. The key secondary endpoints are mentioned in Figure S1. The safety and tolerability were assessed as the proportion of patients with adverse events (AEs) leading to discontinuation of study medication, frequency of AEs and serious AEs over 52 weeks, summarized by preferred term coded by the Medical Dictionary for Regulatory Activities (https://www.meddra.org/how-to-use/support-documentation/korean). In addition, all patients self-monitored and reported symptoms suggestive of hypoglycaemia, which was defined in accordance with the Committee for Proprietary Medicinal Products guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus.[25]

2.4 | Statistical analysis

Efficacy analyses were performed on the full analysis set (FAS), which included all randomized patients who received at least one dose of study medication during the 52-week treatment period with no missing baseline values and at least one post-baseline value for primary efficacy variables. All safety outcome summaries were performed on the safety analysis set (SAF), including patients who received at least one dose of study medication. Per-protocol set was a subset of the FAS consisting of patients who did not violate the terms of the protocol, which may have affected the efficacy endpoints significantly. Statistical Analysis Software version 9.2 or higher was used in all statistical analyses.

The primary endpoint was analysed with an analysis of covariance model with treatment group as a factor and baseline total BF mass as a covariate. The model was used to derive a least squares (LS) estimate of the treatment difference in mean change from baseline with corresponding two-sided 95% confidence interval (CI) and two-sided *p*-value. Furthermore, two-sided 95% CIs for the mean change within each treatment group was calculated. Changes in lean mass, abdominal VAT and SAT areas, high sensitivity C-reactive protein (hs-CRP) and adiponectin were analysed similar to the primary endpoint. Non-parametric methods were used for outcome variables with non-normal distribution.

The secondary endpoints were analysed using mixed model repeated measures or analysis of covariance for continuous variables or logistic regression for binary variables. The proportion of patients who achieved an HbA1c <7.0% at week 52, last observation carried forward were assessed using logistic regression analysis. All secondary endpoints were interpreted descriptively, without significance testing. Changes from baseline to 52 weeks for each clinical laboratory test

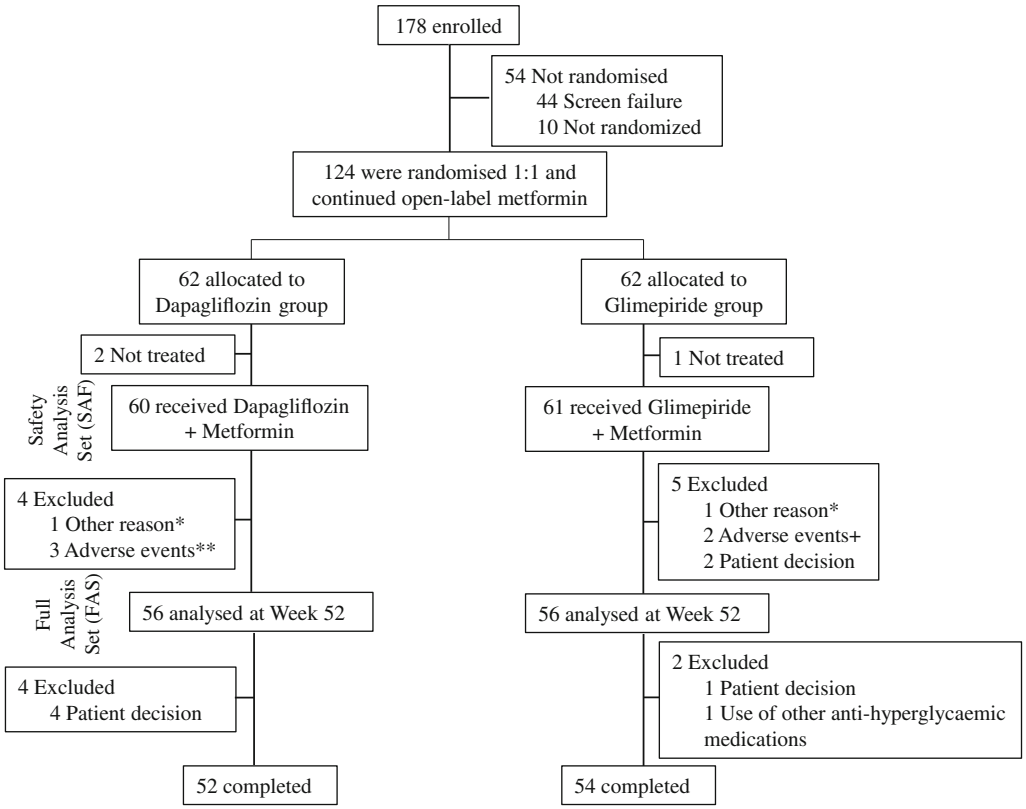

FIGURE 1 Flowchart of patient disposition in the study population. FAS: all randomized patients who received at least one dose of study medication during the 52-week treatment period with no missing baseline values and at least one post-baseline value for primary efficacy variables. *Metal insertion; **genital pruritus, transient ischaemic attack, urinary tract infection; +acute pyelonephritis, upper abdominal pain. FAS, full analysis set.

were summarized using descriptive statistics. Sensitivity analysis was performed to assess the impact of gender on primary and secondary endpoints.

3 | RESULTS

In total, 178 patients were screened, of which 124 were randomized in the study; three patients were randomized but did not receive the study treatment (two in dapagliflozin; one in the glimepiride groups). Overall, 121 patients receiving study treatment were included in the SAF population; 106 (85.5%) patients completed the study (Figure 1). The FAS group included 112 patients (56 each in the dapagliflozin and glimepiride groups) after excluding nine patients. Fourteen (11.3%) patients discontinued the study treatment prematurely.

3.1 | Baseline characteristics

Overall, the mean ± SD age was 55.1 ± 9.1 years; 55.4% (n = 62) of patients were men (Table 1); baseline characteristics in the SAF were similar across both treatment groups. The mean ± SD duration of T2D in the total population was 6.2 ± 4.9 years, with a mean ± SD HbA1c of 8.0 ± 0.7% and mean ± SD FBG of 156.0 ± 31.7 mg/dl. The mean body weight and BMI in the total population were marginally higher in the dapagliflozin group (73.0 ± 11.6 kg and 27.0 ± 3.2 kg/m^2, respectively). In total, 12.4% (n = 15/121) patients took rescue medication during the study, and 94.2% (n = 114/121) were on concomitant medications. Atorvastatin and metformin were the most common concomitant medication and sitagliptin was the most commonly used rescue medication (Table S2).

3.2 | Body composition

Overall, the mean total BF mass and total BF% were 23.5 ± 6.6 kg and 33.6 ± 7.2%, respectively, with similar distribution between in the two groups. While the total lean body mass (overall: 45.3 ± 8.9 kg) and the mean VAT area (overall: 139.1 ± 52.2 cm^2) were similar across the two categories, the mean SAT area was higher in the glimepiride group (187.3 ± 66.8 cm^2) compared with the dapagliflozin group (170.0 ± 74.6 cm^2).

3.3 | Diabetes-related comorbidities and complications

At baseline, nearly half (n = 61; 50.4%) of the overall study population had dyslipidaemia and 47.1% (n = 57) had hypertension.

TABLE 1 Baseline characteristics of study participants according to treatment (FAS subset)

	Dapagliflozin + MET (N = 56)	Glimepiride + MET (N = 56)	Total (N = 112)	*p*-Value
Age, years; mean ± SD	54.8 ± 9.0	55.5 ± 9.3	55.1 ± 9.1	.704
Gender, n (%)				
Male	36 (64.3)	26 (46.4)	62 (55.4)	.057
Female	20 (35.7)	30 (53.6)	57 (44.6)	
Ethnicity[a], n (%)				
Korean	60 (100)	61 (100)	121 (100)	N/A
Duration of T2D, years; mean ± SD	6.0 ± 4.8	6.5 ± 4.9	6.2 ± 4.9	.608
HbA1c, %; mean ± SD	8.0 ± 0.7	8.0 ± 0.7	8.0 ± 0.7	.886
FBG, mg/dl; mean ± SD	157.8 ± 35.1	154.2 ± 28.0	156.0 ± 31.7	.543
Systolic BP, mmHg; mean ± SD	126.3 ± 13.4	126.8 ± 10.6	126.5 ± 12.0	.827
Diastolic BP, mmHg; mean ± SD	79.5 ± 8.2	79.3 ± 7.5	79.4 ± 7.8	.895
Physical measurements, mean ± SD				
Body weight, kg	73.0 ± 11.6	70.6 ± 12.8	71.8 ± 12.2	.302
BMI, kg/m^2	27.0 ± 3.2	26.7 ± 3.6	26.8 ± 3.4	.677
Waist circumference, cm	91.5 ± 8.1	91.1 ± 8.9	91.3 ± 8.5	.796
Body composition measurements, mean ± SD				
Total body fat mass, kg	23.6 ± 6.7	23.4 ± 6.5	23.5 ± 6.6	.869
Total body fat, %	33.1 ± 7.3	34.1 ± 7.1	33.6 ± 7.2	.475
Total body lean mass, kg	46.3 ± 8.4	44.4 ± 9.4	45.3 ± 8.9	.262
VAT area, cm^2	139.1 ± 47.2	139.1 ± 57.5	139.1 ± 52.2	.994
SAT area, cm^2	170.0 ± 74.6	187.3 ± 66.8	178.5 ± 71.0	.211
Diabetes-related diseases, n (%)				
Neuropathy	8 (14.3)	8 (14.3)	16 (14.3)	N/A
Retinopathy	2 (3.6)	4 (7.1)	6 (5.4)	N/A
Nephropathy	1 (1.8)	1 (1.8)	2 (1.8)	N/A
Vascular disorder	1 (1.8)	1 (1.8)	2 (1.8)	N/A
Hypertension, n (%)	24 (42.9)	25 (44.6)	49 (43.8)	N/A
Dyslipidaemia, n (%)	28 (50.0)	27 (48.2)	55 (49.1)	N/A
hs-CRP, mg/L; mean ± SD	2.33 ± 6.00	1.14 ± 1.58	1.73 ± 4.41	.154
Adiponectin, ng/ml; mean ± SD	4441 ± 3804	5194 ± 2395	4817 ± 3186	.212
Medical history[a], n (%)				
Patients with cardiac disorders	2 (3.3)	5 (8.2)	7 (5.8)	N/A
Renal and urinary disorders	7 (11.7)	6 (9.8)	13 (10.7)	N/A
Use of diuretics[a], n (%)				
Hydrochlorothiazide	0	2 (3.3)	2 (1.7)	N/A

Note: Values are presented as mean ± SD or n (%). Efficacy analyses were performed on FAS, which included all randomized patients who received at least one dose of study medication during the 52-week treatment period with no missing baseline values and at least one post baseline value for primary efficacy variables.

Abbreviations: BMI, body mass index; BP, blood pressure; FAS, full analysis set; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; hs-CRP, high sensitivity C-reactive protein; MET, metformin; n, number of patients; N/A, not applicable; SAT, subcutaneous adipose tissue; SD, standard deviation; T2D, type 2 diabetes; VAT, visceral adipose tissue.

[a]Safety analysis set.

Neuropathy (n = 18; 14.9%) was the most commonly reported complications, while 5.8% (n = 7) and 23.1% (n = 28) patients had cardiac disorders (angina pectoris/coronary artery disease) and arteriosclerosis, respectively.

3.4 | Primary efficacy endpoint

The BF mass LS mean reduced significantly from baseline to week 52 for dapagliflozin (−1.49 kg [95% CI −2.03 to −0.95]) compared

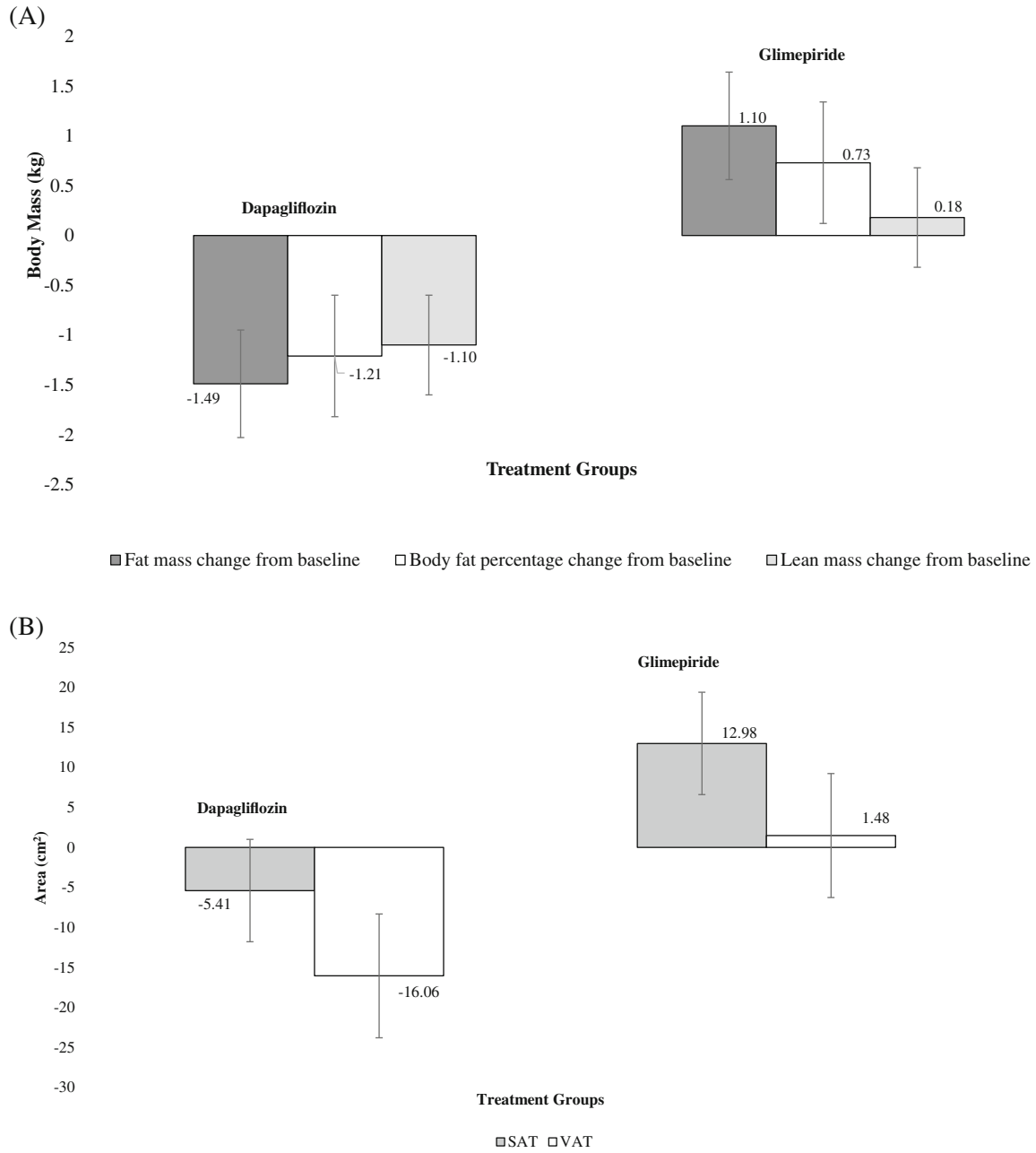

FIGURE 2 Change in body composition and adipose tissue area at week 52. (A) Change in body composition at week 52. Difference between mean estimate of dapagliflozin and glimepiride for total body fat mass (kg) = −2.59 (95% CI −3.34 to −1.82); $p < .001$. Difference between mean estimate of dapagliflozin and glimepiride for total body lean mass (kg) = −1.28 (95% CI −1.99 to −0.56); $p < .001$. (B) Change in adipose tissue area at week 52. Difference between LS mean estimate of dapagliflozin and glimepiride for VAT area (cm^2) = −17.55 (95% CI −28.60 to −6.49); $p < .001$. Difference between LS mean estimate of dapagliflozin and glimepiride for SAT area (cm^2) = 18.39 (−27.56 to −9.22); $p < .001$. VAT/SAT ratio mean change from baseline week 52 for dapagliflozin was −0.05 (−0.115 to 0.017) versus −0.02 (−0.084 to 0.050) for glimepiride; the VAT/SAT ratio LS mean difference was −0.03 (−0.127 to 0.063; $p = .503$). The lean-to-body mass between the two arms was maintained from baseline to week 52 (baseline: 0.63 vs. 0.63, Week 52: 0.63 vs. 0.63). LS, least squares; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

with glimepiride (+1.10 kg [95% CI 0.56-1.64]); there was a significant LS mean difference between the two groups −2.58 kg (95% CI −3.35 to −1.82; $p < .001$) (Figure 2A). Similarly, at week 52, the BF % LS mean reduced significantly from baseline for dapagliflozin (−1.21% [95% CI −1.82 to −0.60]) compared with glimepiride (0.73% [95% CI 0.12-1.34]); the difference in LS mean change between the two groups was −1.94% (95% CI −2.81 to −1.08; $p < .001$). We also observed a significant decrease in the total lean body mass for the dapagliflozin group from baseline to the end of week 52 (difference in the LS mean change between the two

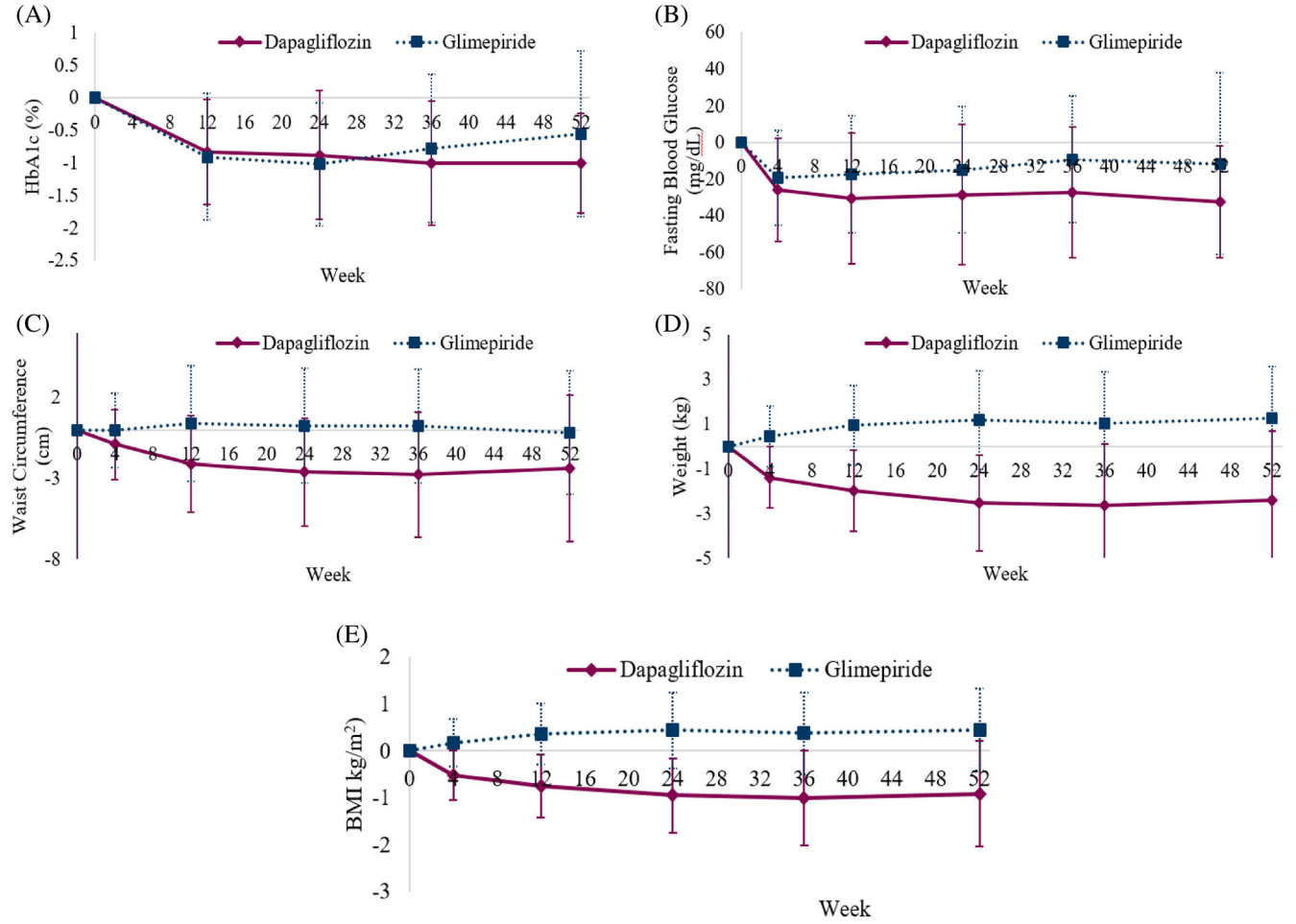

FIGURE 3 Change in secondary endpoints at week 52: HbA1c (%), FBG (mg/dl), waist circumference (cm), weight (kg) and BMI (kg/m^2). BMI, body mass index; FBG, fasting blood glucose, HbA1c, glycated haemoglobin.

groups was −1.28 kg [95% CI −1.99 to −0.56]; $p < .001$) (Figure 2A). The VAT and SAT areas also showed significant decreases in the dapagliflozin group as compared with glimepiride; difference in the LS mean change for VAT was −17.55 cm^2 (95% CI −28.60 to −6.49; $p = .002$) and SAT was −18.39 cm^2 (95%CI −27.56 to −9.22; $p < 0.001$; Figure 2B). The VAT/SAT ratio mean change in the FAS population from baseline to week 52 for dapagliflozin was −0.05 (−0.115 to 0.017) versus −0.02 (−0.084 to 0.050) for glimepiride; the VAT/SAT ratio LS mean difference was −0.03 (−0.127 to 0.063; $p = .503$). The lean-to-body mass between the two arms was maintained at end of therapy from baseline (baseline: 0.63 vs. 0.63, week 52: 0.63 vs. 0.63).

The sensitivity analysis for total BF mass and total BF% with gender as a covariate showed robustness of the results and confirmed that dapagliflozin had a statistically significant effect in reducing total BF mass and total BF% as compared with glimepiride at week 52. The sensitivity analysis for total BF mass in the FAS population with gender as a covariate ($p = .340$) showed dapagliflozin LS mean difference from glimepiride at week 52 of −2.7 kg (95% CI −3.432 to −1.876; $p < .001$). The sensitivity analysis for total BF% in the FAS population with gender as a covariate ($p = .744$) showed at week 52 dapagliflozin LS mean difference from glimepiride of −1.97% (95% CI −2.854 to −1.090; $p < .001$).

3.5 | Secondary efficacy endpoints

The mean change in HbA1c from baseline to week 52 for dapagliflozin was −1.00% (95% CI −1.259 to −0.745) versus −0.54% (95% CI −0.802 to −0.287) for glimepiride; the difference was statistically significant between the two groups −0.46% (95% CI −0.821 to −0.094; $p = .014$). The effect of dapagliflozin on glycaemic control was shown at week 12 and sustained throughout the study period (Figure 3). The initial drop in HbA1c with glimepiride was greater than observed with dapagliflozin; however, glycaemic control with glimepiride waned from week 24 onwards but remained stable for dapagliflozin (Figure 3A). Reductions in HbA1c and FBG were significantly greater with dapagliflozin compared with glimepiride, and this trend of glucose-lowering effect of dapagliflozin was maintained until week 52 (Table 2, Figure 3). The proportion of patients who achieved glycaemic response (HbA1c <7%) at week 52 was more in the dapagliflozin group (n = 27, 48.2%) as compared with the glimepiride group

(n = 22, 39.3%) in the FAS population. The point estimate and 95% CI of odds ratio at week 52 was 1.45 (95% CI 0.673-3.113; $p = .343$).

3.6 | Other key endpoints

Dapagliflozin use was associated with a significant reduction in the total body weight, waist circumference and BMI compared with glimepiride; the LS mean differences between the groups were −3.7 kg (95% CI −4.667 to −2.631), −2.21 cm (95% CI −3.785 to −0.635), −1.37 kg/m^2 (95% CI −1.742 to −0.990); p-value for all the variables <.01, respectively (Table 2). The changes in systolic blood pressure (SBP) significantly favoured dapagliflozin compared with glimepiride ($p = .002$); however, no difference between the dapagliflozin and the glimepiride groups were noted for diastolic blood pressure (Table 2).

TABLE 2 Key secondary endpoints at week 52

	Dapagliflozin + MET (N = 56)	Glimepiride + MET (N = 56)
Weight (kg)		
Baseline, mean ± SD	73.0 ± 11.6	70.6 ± 12.8
Adjusted mean change from baseline (95% CI)	−2.38 (−3.10, −1.66)	1.26 (0.55, 1.98)
Difference from glimepiride + MET (95% CI)	−3.65 (−4.67, −2.63)	
p-Value of difference	<.001	
Waist circumference (cm)		
Baseline, mean ± SD	91.5 ± 8.1	91.1 ± 8.9
Adjusted mean change from baseline (95% CI)	−2.37 (−3.48, −1.25)	−0.16 (−1.27, 0.96)
Difference from glimepiride + MET (95% CI)	−2.21 (−3.79, −0.63)	
p-Value of difference	.006	
BMI (kg/m^2)		
Baseline, mean ± SD	27.0 ± 3.2	26.7 ± 3.6
Adjusted mean change from baseline (95% CI)	−0.91 (−1.17, −0.64)	0.46 (0.19, 0.73)
Difference from glimepiride + MET (95% CI)	−1.37 (−1.74, −0.99)	
p-value of difference	<.001	
HbA1c (%)		
Baseline, mean ± SD	8.0 ± 0.7	8.0 ± 0.7
Adjusted mean change from baseline (95% CI)	−1.00 (−1.26, −0.75)	−0.54 (−0.80, −0.29)
Difference from glimepiride + MET (95% CI)	−0.46 (−0.82, −0.09)	
p-Value of difference	.014	
Proportion of patients with HbA1c <7%	48.2%	39.3%
FBG (mg/dl)		
Baseline, mean ± SD	157.8 ± 35.1	154.2 ± 28.0
Adjusted mean change from baseline (95% CI)	−30.94 (−40.08, −21.80)	−12.70 (−21.79, −3.61)
Difference from glimepiride + MET (95% CI)	−18.25 (−31.14, −5.35)	
p-value of difference	.006	
Systolic BP (mmHg)		
Baseline, mean ± SD	126.3 ± 13.4	126.8 ± 10.6
Adjusted mean change from baseline (95% CI)	−2.18 (−5.12, 0.77)	4.63 (1.68, 7.57)
Difference from glimepiride + MET (95% CI)	−6.81 (−10.97, −2.64)	
p-Value of difference	.002	
Diastolic BP (mmHg)		
Baseline, mean ± SD	79.5 ± 8.2	79.3 ± 7.5
Adjusted mean change from baseline (95% CI)	−0.25 (−2.52, 2.02)	2.36 (0.09, 4.64)
Difference from glimepiride + MET (95% CI)	−2.61 (−5.83, 0.60)	
p-Value of difference	.110	

TABLE 2 (Continued)

	Dapagliflozin + MET (N = 56)	Glimepiride + MET (N = 56)
Adiponectin (ng/ml)		
Baseline, mean ± SD	4441 ± 3804	5194 ± 2395
Adjusted mean change from baseline (95% CI)	1746.66 (1296.14, 2197.18)	1088.95 (638.43, 1539.47)
Difference from glimepiride + MET (95% CI)	657.71 (18.32, 1297.10)	
p-Value of difference	.044	
hs-CRP (mg/L)		
Baseline, mean ± SD	2.33 ± 6.00	1.14 ± 1.58
Adjusted mean change from baseline	−0.51 (−1.03, 0.01)	−0.39 (−0.91, 0.13)
Difference from glimepiride + MET (95% CI)	−0.12 (−0.86, 0.63)	
p-Value of difference	.756	

Note: Difference = least squares mean estimate for dapagliflozin − least squares mean estimate for glimepiride. *p*-Value computed from mixed model repeated measures model: change from baseline = treatment + visit + treatment × visit + baseline value. Efficacy analyses were performed on a full analysis set, which included all randomized patients who received at least one dose of study medication during the 52-week treatment period with no missing baseline values and at least one post baseline value for primary efficacy variables.

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; hs-CRP, high sensitivity C-reactive protein; MET, metformin; SD, standard deviation.

3.7 | Safety and tolerability

Overall, 52 (43.0%) patients reported AEs during the study period; incidences were similar across both the treatment groups. Of patients with reported AEs, most (32 of 52; 61.5%) were mild in intensity. AEs that were considered causally related to study treatment were reported in about 14.0% (n = 17) of patients. Serious AEs were reported in 9.9% (n = 12) patients and none of them were considered related to the study treatment. Occurrence of AEs led to permanent discontinuation of study treatment in five patients, and one patient discontinued because of initiation of another anti-hyperglycaemic agent. The most frequently reported AEs (in >1% of patients) were: hypoglycaemia (n = 10; 8.3%); nasopharyngitis (n = 6; 5%); toothache (n = 5; 4.1%); cystitis (n = 2; 1.7%); gastroesophageal reflux disease (n = 2; 1.7%); and chronic gastritis (n = 2; 1.7%) (Table S3). Of 15 hypoglycaemic events reported, the majority (12 events) occurred in the glimepiride treatment group; none of them led to study discontinuation. The incidence of gastrointestinal disorders was similar in both treatment groups. One patient in the dapagliflozin treatment group reported genitourinary infection.

4 | DISCUSSION

To our knowledge, this prospective, randomized, clinical study is one of the robust analyses, evaluating the effects of dapagliflozin compared with glimepiride on body composition in Korean patients with T2D post metformin failure. Our study results showed that the 52-week treatment with dapagliflozin significantly reduced total BF mass, total BF%, lean body mass, and VAT and SAT areas, compared with glimepiride. In addition, this study highlighted the significant role of dapagliflozin for other favourable clinical outcomes compared with glimepiride, in reducing body weight, waist circumference, BMI, blood pressure and increasing adiponectin.

Our study showed that dapagliflozin had a statistically significant effect in reducing total BF mass (−1.49 kg) and total BF% (−1.21%) over 52 weeks compared with baseline. Results from the sensitivity analysis for the total BF mass and total BF% with gender as a covariate showed robustness of the results and confirmed dapagliflozin had a statistically significant effect in reducing the total BF mass and total BF% as compared with glimepiride. Data from previous clinical trials have reported that dapagliflozin leads to reduced BF and weight loss – either as monotherapy, or in combination with other medications such as metformin, glimepiride, or insulin.[13–16] Real-world studies from both developed and developing countries have also substantiated the benefit of dapagliflozin for weight loss in patients with T2D.[26–29] However, the unique phenotype of the Asian population constituting higher BF at lower BMI makes it imperative to crystallize the implications of dapagliflozin, specifically with respect to the total BF mass and total BF%. The results of our study in the Korean population affirms the multi-pronged approach of dapagliflozin on body composition, even in characteristic 'thin-fat' phenotypes. The total weight change by dapagliflozin in our study (−2.38 kg) was marginally less compared with the study in White people (−2.96 kg, 95% CI −3.51 to −2.41).[29] Notably, in the study about White people, the reduction in fat mass accounted for two-thirds of the total weight loss observed with dapagliflozin, an observation similar to our study. In a study conducted in an Asian population, Sasaki et al. evaluated moderately obese Japanese patients with T2D treated with luseogliflozin for a year[30]. The total BF mass significantly decreased early in the treatment (−0.5 kg at week 4) and continued until week 24 [−1.97 kg (95% CI −2.66 to −1.28)]. The visceral fat area at week 24 showed an average downward trend, although this was not significant. The skeletal muscle mass

index showed a significant but small change at and after week 36.[30] Similar results were observed in our study with a reduction in body weight of 1.3 kg from baseline to week 4 and a further reduction at week 24 (−2.5 kg).

Another study by Sugiyama et al.[31] in Japanese patients with T2D reported a higher reduction in fat mass (−3.1 ± 2.6 kg; $p < .01$) and BF % (−2.7 ± 2.9%; $p < .01$) over 24 weeks of dapagliflozin use compared with non-SGLT-2i therapy. However, the study measured body composition by bioelectrical impedance analysis, which estimates body composition with lower accuracy than DXA used in our study and the study conducted by Sasaki et al.[30] Similar to our results, a recent real-world analysis (n = 140) among obese patients with T2D from Korea, reported significant decrease in total body weight (from 83.01 ± 16.42 to 79.70 ± 16.13 kg), BMI (from 30.3 ± 4.7 to 29.1 ± 4.7 kg/m^2), BF mass (from 31.09 ± 9.90 to 28.31 ± 9.91 kg) and BF% (from 36.75% ± 7.56% to 35.12% ± 7.19%; $p < .001$) with dapagliflozin monotherapy for 6 months. These results indicate that Korean patients with T2D prescribed with dapagliflozin may have weight reduction, predominantly driven by BF mass loss.[32]

The amount of visceral fat correlates with insulin resistance and has strong associations with diabetes, metabolic syndrome and increased cardiovascular risk.[33–35] As the preferential distribution of fat in visceral depots has been observed in Asian populations, compared with White people, it is recommended to use a lower BMI level as a practical cut-off for estimating the risk of T2D and cardiovascular disease.[36,37] In our study, dapagliflozin significantly reduced the VAT area (−16.06 cm^2) more predominantly than the SAT area (−5.41 cm^2) from baseline to week 52. A recent study in White people evaluating the effects of dapagliflozin plus saxagliptin plus metformin versus glimepiride plus metformin on VAT and SAT areas reported a >10% reduction in adipose tissue volumes ($p < .01$) with the former combination therapy of dapagliflozin. However, the study reported similar reductions in both SAT and VAT volumes, in contrast with our study and revealed a significant reduction in liver fat.[38] Other SGLT-2is such as ipragliflozin have reported visceral fat loss in Japanese patients with T2D under adequate diet therapy; however, loss of skeletal mass was also observed.[39] Another study evaluating the effects of tofogliflozin on body composition revealed that the reduction in BF mass, visceral fat area and skeletal muscle mass was because of the loss of total body water and intracellular and extracellular water, which may have been related with the reduction of body weight.[40] In a study performed to evaluate the effect of dapagliflozin versus glibenclamide on the ratio of lean-to-total mass in patients with T2D, it was found that dapagliflozin reduced total body mass but increased the ratio of lean-to-total mass that was because of a more intensive reduction in fat mass than in lean mass implying that dapagliflozin causes improvement of skeletal muscle metabolism (skeletal muscle mass index, SMI).[41] Similarly, in the study conducted by Sasaki et al., the SMI decreased over the course of the treatment, but the degree of the change was small. In our study, the lean-to-body mass between the two arms was maintained at end of therapy. To maintain optimal levels of skeletal muscle mass during the T2D treatment with SGLT-2i, further investigations and close monitoring of patients are required. The role of diet counselling and management are crucial particularly in the early stages of treatment up to week 36, during which period drastic changes in the metabolism are followed by changes in the SMI.

Our study showed a statistically significant increase in adiponectin levels with dapagliflozin compared with glimepiride with a mean difference of 657.71 ng/ml (95% CI: 18.33-1297.10, $p = .044$); adiponectin, an emerging insulin-sensitizing adipokine has a direct correlation with insulin secretion and is known to improve insulin resistance.[42] The statistically significant increase in adiponectin levels suggests improved insulin resistance levels in the dapagliflozin arm. The decrease in hs-CRP with dapagliflozin use was statistically insignificant. A study in an outpatient clinic for diabetes in Japan showed significant decrease in hs-CRP (ng/ml) (from 2410 ± 2814 to 1607 ± 1960; $p < .01$) with significant increase in adiponectin (μg/ml) (from 5.1 ± 2.3 to 6.7 ± 4.2; $p < .01$) following monotherapy with dapagliflozin, among a small number of obese patients with T2D (n = 27).[43] A meta-analysis showed that SGLT-2i treatment is associated with decreased circulating leptin levels and increased circulating adiponectin levels, which might contribute to the beneficial effects of SGLT-2i on metabolic homeostasis.[44]

In our study alongside significant reductions in HbA1c levels, the proportion of patients who achieved glycaemic response (HbA1c <7%) was more in the dapagliflozin group (48.2%) as compared with the glimepiride group (39.3%). SUs are designed to be used at a lower dosage and they can potentially lose glycaemic durability as early as 6 months to 1 year.[45] Similar to our study, data from real-world clinical practice in patients with T2D in Korea who started SGLT-2i (empagliflozin or dapagliflozin) as add-on or switch therapy, show significant reductions in mean adjusted HbA1c (−0.68%; $p < .001$) in overall patients, at week 12. The proportion of patients who achieved HbA1c <7.0% was 18.3% in overall patients, 23.7% in the add-on group, and 12.8% in the switch group ($p = 0.004$). Comparable with our study, significant reductions were also observed in FBG, SBP and diastolic blood pressure.[46]

Our study showed that dapagliflozin was generally well tolerated with no new safety concerns. The majority (80%) of the hypoglycaemic events were reported in the glimepiride group. Because of its insulin independent mode of action, dapagliflozin has a low intrinsic risk of hypoglycaemia. In the dapagliflozin group, one patient reported AEs such as urinary tract infection, urinary retention, urethritis and genital infection. A meta-analysis revealed that dapagliflozin exhibits an increased risk of urinary tract infection (relative risk 1.21; 95% CI 1.02-1.43).[47,48]

This study had few limitations as we did not collect data on lifestyle indicators such as patients' daily diet or physical activity, which can have an effect on body weight. Having data on food intake pattern and energy expenditure could provide better insights into the mechanism of weight change. The male/female ratio was different between the two groups; however, it did not affect the results as shown in the sensitivity analysis. Objective evaluation of insulin resistance using models such as HOMA-IR was not included in the study design to ascertain the difference in treatment effect. The selection of

SU as the comparator arm was another limitation, as their usage is generally designed for at a low dosage. Furthermore, SU seemed to lose glycaemic durability at 1 year, necessitating the addition of another therapy. However, this is a pioneering study evaluating the effect of dapagliflozin compared with glimepiride as the add-on to metformin on body composition among the Asian population.

5 | CONCLUSION

The BEYOND study confirms the statistically significant effects of dapagliflozin compared with glimepiride as the add-on to metformin in reducing total BF mass and total BF% at week 52 among Korean population with T2D. Dapagliflozin was also associated with reductions in lean body mass, VAT and SAT areas, and SBP over the study period. Dapagliflozin showed better glycaemic control and increased adiponectin with fewer hypoglycaemic episodes. Being safe and well tolerated, dapagliflozin is a potential valuable alternative to SUs as add-on after metformin monotherapy failure in Korean and other Asian people with T2D.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

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