Effects of intensive exercise combined with dapagliflozin on body composition in patients with type 2 diabetes: a randomized controlled trial

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Abstract. This study was aimed to evaluate the effects of intensive exercise in addition to the administration of sodium-glucose cotransporter 2 inhibitor dapagliflozin (DAPA) on body composition, including fat-free mass, in type 2 diabetes. We randomly assigned 146 patients to 24 weeks of treatment with intensive exercise, including resistance training, plus 5 mg (up to 10 mg) of DAPA daily (IT group) or DAPA alone (CT group). The primary endpoint was the difference in the change in fat-free mass from baseline to 24 weeks between the groups. The skeletal muscle mass index (SMI); metabolic profile, including HbA1c; and regional fat mass were also determined. ANCOVA was used for the group comparison, with least squares mean (LSM) differences and 95% confidence interval (CI). There was no significant difference in the change in fat-free mass (LSM difference –0.1 kg (95% CI: –0.5 to 0.4) and SMI (LSM difference –0.1 kg (95% CI: –0.2 to 0.1) between the groups. In contrast, the reduction of trunk fat mass was significantly higher in the IT group than in the CT group ((LSM difference –0.5 kg [95% CI –0.9 to –0.1]). Higher adherence to the resistance training tended to be associated with changes in HbA1c and high-sensitivity CRP levels. Our study suggests that intensive exercise do not prevent the reduction of fat-free mass after administration of SGLT2 inhibitors but can increase the reduction in abdominal fat, presumably leading to further improvements of hyperglycemia and chronic inflammation than DAPA alone in type 2 diabetes patients.

Key words: Exercise, Dapagliflozin, Dual-energy X-ray absorptiometry, Body composition, Type 2 diabetes

SODIUM-GLUCOSE Cotransporter 2 (SGLT2) inhibitors block glucose reabsorption in the proximal tubules of the kidneys, leading to increased glucose excretion and decreased plasma glucose levels. Recent large-scale clinical trials have shown beneficial effects of these drugs on cardiorenal events in patients with type 2 diabetes who had or were at a high risk for cardiovascular disease [1-4], and a meta-analysis including these trials [1-3] confirmed a significant reduction of cardiovascular and renal events and hospitalization for heart failure [5]. Based on these findings, the American Diabetes Association and the European Association for the Study of Diabetes proposed a new approach for the treatment of type 2 diabetes, recommending SGLT2 inhibitors with proven cardiovascular and renal benefits as a second-line medication for patients with atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease [6, 7].

Regarding the possible mechanism of cardiorenal protection of SGLT2 inhibitors, a favorable impact of these agents on the body composition has been suggested, in addition to the metabolic benefits (improvement of hyperglycemia and dyslipidemia), a reduction in blood pressure, increased natriuresis, the preservation of kidney function, and direct effects on myocardium [8, 9].
SGLT2 inhibitors can reduce weight, especially body fat, including visceral [10, 11], hepatic [12, 13], and epicardial [14, 15] fat accumulation, in patients with type 2 diabetes. These changes in adipose tissue by SGLT2 inhibitors may lead to a reduction in cardiovascular events.

Apart from the beneficial effects of SGLT2 inhibitors on adipose tissue, it has also been reported that non-fat mass is reduced by SGLT2 inhibitors [10, 16-18]. In Japanese patients with type 2 diabetes, a small but significant reduction in skeletal muscle mass index (SMI) and protein content evaluated using bioelectrical impedance analysis was observed after the administration of ertugliflozin [19]. Luseogliflozin was also reported to significantly reduce SMI, evaluated using dual-energy X-ray absorptiometry (DXA) [20]. As SGLT2 inhibitors have the potential to substantially reduce the risk of heart failure in elderly patients with type 2 diabetes, who are at an extremely high risk of sarcopenia/frailty [21, 22], strategies to preserve muscle mass and function should be established when using SGLT2 inhibitors, especially in elderly patients with diabetes. Therefore, we conducted a randomized controlled trial (RCT) to investigate whether intensive physical training, including resistance exercise and aerobic exercise, can reduce the risk of reduction in muscle mass after administration of SGLT2 inhibitors in patients with type 2 diabetes.

**Materials and Methods**

**Study design and participants**

We performed a multicenter, open-label, parallel-group RCT to investigate whether resistance training, in addition to the administration of SGLT2 inhibitor dapagliflozin (DAPA), could prevent the loss of muscle mass in patients with type 2 diabetes at six centers in Japan (Kyushu University Hospital, Fukuoka; Tokyo Medical and Dental University Hospital, Tokyo; Kohokai Takagi Hospital, Fukuoka; Saiseikai Iizuka Kaho Hospital, Fukuoka; Federation of National Public Service Personnel Mutual Aid Associations Hamanomachi Hospital, Fukuoka; Iizuka Hospital, Fukuoka). This study complies with the principles established by the Declaration of Helsinki, and the study protocol was approved by the institutional review boards or independent ethics committees at the participating institutions. The eligibility of participants was determined by the investigators according to the inclusion and exclusion criteria (Table 1). All participants provided written informed consent prior to participation. This study was initially registered with University Hospital Medical Information Network Clinical Trials Registry (UMIN000020263) and was re-registered with Japan Registry of Clinical Trials (jRCT) (jRCTs071180050) because the specific clinical research included in this study required registration with jRCT due to the Clinical Research Law enforcement in Japan that was implemented on April 1, 2018.

**Randomization**

As shown in Fig. 1, participants were randomly assigned (1:1) using dynamic allocation by the minimization method to either DAPA 5 mg daily with intensive exercise therapy, including resistance training, (IT group) or DAPA 5 mg daily with usual care (CT group). The allocation factor was stratified by age (≥20 to <65 years old vs. ≥65 to <75 years old), gender, body mass index (BMI; ≥18.5 to <25.0 kg/m² vs. ≥25.0 to <35.0 kg/m²). The method of allocation concealment was central registration using an interactive web response system.

**Procedures**

DAPA was administered from a starting dose of 5 mg to both groups, and participants were allowed to increase the dose up to 10 mg after ≥4 weeks if they failed to achieve the target HbA1c of <7.0% (Fig. 2). The treating physicians had sole discretion on prescribing other glucose-lowering agents.

Participants in the CT group were encouraged to walk ≥6,000 steps daily with a pedometer (HJ-005; Omron Healthcare, Kyoto, Japan) throughout the trial. To evaluate the walking intensity without participants’ awareness, they wore a walking intensity monitor (Medi Walk MT-KT02DZ; Terumo, Tokyo, Japan) with masking. They were free to undergo resistance training, but this was not supervised by the physician. They kept a walking logbook daily.

Participants in the IT group were encouraged to walk ≥8,000 steps daily, with physical exercise of ≥3.0 metabolic equivalents of task (METS) for ≥30 min per day. Both steps and METS values were evaluated using a walking intensity monitor (Medi Walk MT-KT02DZ). Additionally, they underwent resistance training of three sets of 10 repetitions daily throughout the intervention period. Each training session consisted of six items, including (1) squats, (2) push-ups, and exercise regarding (3) shin muscle, (4) quadriceps, (5) abdominal muscle, and (6) latissimus dorsi, gluteus maximus, and hamstring muscle. The resistance training aimed to be practical and able to be done at home without any assistance from an instructor. Prior to and after the resistance training, the participants did a warm-up and cool-down. If the participants were unable to perform 10 repetitions in the first set of each item, the training load was decreased. If the participants could complete all the daily training, they were allowed to increase the sets or repetitions of each item according to their own judgment. They
kept an activity logbook daily to plot a line graph of their weight and to complete a table of their resistance training. Every 4 weeks throughout the trial, trained counselors inspired the participants face-to-face or by phone to continue exercising by assessing the exercise situation and the change in weight and each consultation took about 10 min.

The exercise achievement rate was calculated based on the following definitions: step counts, ≥6,000 daily in the CT and ≥8,000 daily in the IT group; activity time of ≥3.0 METS; ≥30 min/day; resistance training, ≥60% of the total amount of training.

The schedule of data collection is summarized in Fig. 2. Participants regularly visited their outpatient clinic and received diabetes education at each visit. Blood and urine samples and information on medication were collected at baseline and at 4, 8, 12, and 24 weeks.

**Laboratory assays**

HbA1c was measured using high-performance liquid chromatography according to the Japan Diabetes Society method and was converted to the National Glycohemoglobin Standardization Program values [23]. The measurement of serum creatinine and urinary albumin concentrations in a spot urine sample, calculation of urinary albumin to creatinine ratio (ACR; mg/g), and estimation of glomerular filtration rate have been detailed elsewhere [24]. Adiponectin, leptin, interleukin-6 (IL-6), high-sensitivity tumor necrosis factor-alpha (hsTNF-α), and high-sensitivity C-reactive protein (hsCRP) were measured using latex immunoturbidimetric assay, radioimmunoassay, chemiluminescent enzyme immunoassay, enzyme-linked immunosorbent assay, and latex immunoturbidimetric assay, respectively. The measurements of these cytokines were conducted by SRL (Tokyo, Japan).

**Table 1  Inclusion and exclusion criteria**

| Inclusion criteria                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Type 2 diabetes aged ≥20 and <75 years old                                                                                                                                                                                                                                                                                                       |
| 2. Body mass index ≥18.5 kg/m² and <35.0 kg/m²                                                                                                                                                                                                                                                                                                    |
| 3. HbA1c ≥6.5% and <10.0%                                                                                                                                                                                                                                                                                                                           |
| 4. eGFR ≥45.0 mL/min/1.73 m²                                                                                                                                                                                                                                                                                                                         |
| 5. No change in diabetes treatment for 8 weeks or longer prior to the allocation                                                                                                                                                                                                                                                                     |
| 6. Be able to abide the designated dietary and exercise therapy                                                                                                                                                                                                                                                                                     |
| 7. Informed consent in written form                                                                                                                                                                                                                                                                                                                 |

| Exclusion criteria                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Type 1 diabetes                                                                                                                                                                                                                                                                                                                                  |
| 2. History of hypersensitivity of SGLT2 inhibitors                                                                                                                                                                                                                                                                                                    |
| 3. Severe ketosis, diabetic coma, or precoma                                                                                                                                                                                                                                                                                                          |
| 4. Severe infections, patients before or after operations or having severe external injuries                                                                                                                                                                                                                                                        |
| 5. End stage kidney disease or undergoing dialysis                                                                                                                                                                                                                                                                                                    |
| 6. Severe hepatic disease                                                                                                                                                                                                                                                                                                                             |
| 7. At high risk of dehydration                                                                                                                                                                                                                                                                                                                         |
| 8. Pituitary or adrenal dysfunction                                                                                                                                                                                                                                                                                                                   |
| 9. Malnutrition                                                                                                                                                                                                                                                                                                                                      |
| 10. Alcohol abuse                                                                                                                                                                                                                                                                                                                                     |
| 11. Pregnant or lactating women                                                                                                                                                                                                                                                                                                                        |
| 12. Active infectious diseases                                                                                                                                                                                                                                                                                                                         |
| 13. Malignancies                                                                                                                                                                                                                                                                                                                                     |
| 14. Active proliferative diabetic retinopathy                                                                                                                                                                                                                                                                                                         |
| 15. Glucocorticoid treatment                                                                                                                                                                                                                                                                                                                          |
| 16. Insulin treatment                                                                                                                                                                                                                                                                                                                                  |
| 17. Severe hypoglycemia requiring external assistance for recovery                                                                                                                                                                                                                                                                                    |
| 18. Inappropriate for this study                                                                                                                                                                                                                                                                                                                         |
Assessment of the body composition

Body composition was measured using whole-body DXA with a Lunar iDXA system (GE Healthcare, Madison, WI, USA), Discovery DXA system (Hologic, Inc., Marlborough, MA, USA), or Prodigy DXA system (GE Healthcare, Madison, WI, USA) by certified radiological technologists. The same equipment was used during the study period for each patient. The total and regional fat mass and non-fat mass and the percentage of body fat and fat mass of the android and gynoid regions were measured, and the SMI was calculated as previously described [24]. Briefly, the regions of interest (ROI) of android was defined as the region from pelvis cut (lower boundary) to above the pelvis cut by 20% of the distance from pelvis cut line to neck cut line (upper boundary). ROI of gynoid was defined as the region among the 2× android height, beginning at a distance of 1.5× android height below pelvis cut. SMI was calculated as the following: $\text{SMI} = \frac{\text{fat-free mass in upper and lower extremities, kg}}{\text{height (m)^2}}$.

Outcomes

The primary outcome of this study was the difference in the changes in fat-free mass from baseline to 24 weeks. Key secondary outcomes were the changes in the following variables from baseline to 24 weeks: fat mass,
HbA1c, adiponectin, leptin, IL-6, hsTNF-α, hsCRP, weight, systolic and diastolic blood pressure, and urinary ACR. Steps, activity time of ≥3.0 METS, and resistance training frequency (IT group only) at 24 weeks were also included as secondary outcomes. The safety and tolerability of DAPA and exercise were assessed according to serious adverse events and adverse events of special interest, including hypoglycemia, urinary and genital infections, and fractures.

**Statistical analysis**

The primary hypothesis of this study was that the administration of DAPA with intensive exercise therapy, including resistance training, would cause more of a change in fat-free mass (preserve muscle mass) than DAPA alone from baseline to 24 weeks, and the amount of change in both groups would not be zero. The sample size was calculated on the basis of the two-sample t-test analysis; an estimated 66 patients per group was required to provide approximately 80% power to show superiority of resistance training with DAPA to DAPA alone for the change in fat-free mass, with an assumed difference of 0.9 kg between the two groups and an assumed common standard deviation (SD) of 1.83 kg, both of which were based on the results of a previous study [25]. We assumed that 10% of patients would discontinue the study before week 24; therefore, approximately 73 patients were planned for inclusion in each group. Data analysis was performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA.). Data were presented as mean ± SD, median with interquartile range, or percentage, according to the data distribution. Adiponectin, leptin, and hsCRP were logarithmically transformed to improve normality prior to the analysis. The chi-square test or Fisher’s exact test was used to compare categorical variables between groups. Paired t-test or Wilcoxon signed rank test was used to evaluate the differences between baseline and each time point within the group. In addition, the differences between the groups is analyzed using the t-test, Wilcoxon rank-sum test, and ANCOVA, as appropriate for the data distribution. As age and gender affect fat accumulation and loss of skeletal muscle mass and weight are strongly correlated with parameters for body composition, the baseline value of each parameter for body composition, weight, age, and gender were selected as covariates for ANCOVA. Additionally, the significance level was set to 0.05. Multiple tests were conducted for some evaluation items however; the multiplicity adjustment was not performed because the objective was to conduct exploratory evaluations.

**Results**

**Baseline characteristics**

Between June 2016 and February 2019, we enrolled and randomized 146 participants into an IT group (n = 74) and a CT group (n = 72) (Fig. 1). Five participants were excluded, and 141 participants (72 and 69 in the IT and CT groups, respectively) constituted the safety and full analysis set. Of all the randomized participants, 131 (89.7%) completed the study by August 2019. Table 2 shows baseline characteristics, laboratory data, and medications. There were no significant differences in characteristics, anthropometric data, and laboratory data of the subjects between the IT and CT groups. Other than sulfonylureas, concomitant medications did not differ between the groups. During the study period, sulfonylureas were discontinued in 3 participants in the IT group and its prescription rates were 26.4% and 14.5% in the IT and CT group (p = 0.081) at 24 weeks. Glucose-lowering agents other than sulfonylureas were continued throughout the study.

**Adherence to the interventions**

Table 3 shows step counts and physical activities of moderate or higher intensity (≥3.0 METS) in both groups. Participants in the IT group initially walked significantly more than those in the CT group, but the difference in the step counts between the groups became gradually attenuated. Stepwise decreases in the step counts were observed in both groups. As with step counts, the time for physical activities of ≥3.0 METS was significantly longer in the IT group than that in the CT group in the early phase of the intervention period, and the statistical significance remained unchanged during the study. Finally, the achievement rates of step counts and time for physical activities of ≥3.0 METS slowly decreased throughout the study period in both groups. Adherence to the resistance training in the IT group was 77.8% for the first 4 weeks but decreased to 51.4% at the study end. At baseline, urinary glucose was positive in 36% of the IT group and 26% of the CT group. After 4 weeks, ≥90% of participants in both groups showed glucosuria, and the percentage remained unchanged during the study period (data not shown), suggesting that adherence to the SGLT2 inhibitor was consistently high in both groups.

**Changes in body composition**

Table 4 shows changes in body composition, including the primary endpoint of this study. Weight and BMI were gradually and significantly decreased in both groups (p values for weight and BMI at 4, 8, 12, and 24 weeks versus at baseline were all <0.001), but there were no
Table 2  Clinical characteristics and laboratory data at baseline

|                      | IT group (N = 72) | CT group (N = 69) | p values |
|----------------------|------------------|-------------------|----------|
| **Anthropometry**    |                  |                   |          |
| Age (years)          | 59 ± 10          | 57 ± 11           | 0.164    |
| Gender (% male)      | 63.9             | 62.3              | 0.847†   |
| Height (cm)          | 164 ± 9          | 164 ± 9           | 0.903    |
| Weight (kg)          | 69.8 ± 12.9      | 68.8 ± 13.0       | 0.648    |
| Body mass index (kg/m²) | 25.7 ± 3.5         | 25.5 ± 4.0        | 0.714    |
| SBP (mmHg)           | 136 ± 16         | 131 ± 17          | 0.066    |
| DBP (mmHg)           | 81 ± 11          | 80 ± 11           | 0.553    |
| Duration of diabetes (years) | 10 (6–15)      | 8 (4–13)          | 0.288    |
| Diabetic retinopathy (%) | 15.3           | 14.5              | 0.896†   |
| Fatty liver disease (%) | 58.3            | 56.5              | 0.828†   |
| **Laboratory**       |                  |                   |          |
| HbA1c (%)            | 7.7 ± 0.8        | 7.7 ± 0.8         | 0.720    |
| HbA1c (mmol/mol)     | 60.8 ± 8.3       | 60.3 ± 8.3        | 0.720    |
| Glucose (mmol/L)     | 8.9 ±1.7         | 8.8 ±1.8          | 0.957    |
| AST (U/L)            | 21 (18–28)       | 22 (19–28)        | 0.511    |
| ALT (U/L)            | 25 (17–38)       | 26 (15–45)        | 0.460    |
| γ-GTP (U/L)          | 33 (23–51)       | 38 (26–52)        | 0.453    |
| Triglycerides (mmol/L) | 1.2 (0.9–2.1)   | 1.5 (1.0–2.1)    | 0.244    |
| HDL cholesterol (mmol/L) | 1.5 ±0.4         | 1.4 ± 0.4         | 0.498    |
| LDL cholesterol (mmol/L) | 3.0 ± 0.9       | 3.1 ± 0.8         | 0.754    |
| Uric acid (μmol/L)   | 312 ± 69         | 326 ± 73          | 0.236    |
| Creatinine (μmol/L)  | 63 ± 16          | 65 ± 18           | 0.598    |
| eGFR (mL/min/1.73 m²) | 82.4 ± 15.8     | 82.0 ± 17.9       | 0.879    |
| Urinary ACR (mg/g)   | 15 (8–45)        | 21 (7–52)         | 0.980    |
| Urinary Ketone (%)   | 96/3/1/0/0/0     | 86/10/3/0/0/0     | 0.102†   |
| Urinary Glucose (%)  | 72/3/10/6/4/6   | 80/1/7/3/1/7      | 0.810†   |
| **Medications**      |                  |                   |          |
| Glucose-lowering agents (%) |            |                   |          |
| Sulfonylureas (%)    | 30.6             | 14.5              | 0.023†   |
| Metformins (%)       | 54.2             | 60.9              | 0.421†   |
| Alpha-GIs (%)        | 13.9             | 11.6              | 0.683†   |
| Glinides (%)         | 5.6              | 4.3               | 1.000†   |
| TZDs (%)             | 5.6              | 2.9               | 0.681†   |
| DPP4 inhibitors (%)  | 61.1             | 58.0              | 0.704†   |
| GLP1-RAs (%)         | 5.6              | 5.8               | 1.000†   |
| Antihypertensive agents (%) |        |                   |          |
| ACEIs (%)            | 4.2              | 4.3               | 1.000†   |
| ARBs (%)             | 31.9             | 18.8              | 0.074†   |
| CCBs (%)             | 29.2             | 24.6              | 0.545†   |
| Alpha blockers (%)   | 0.0              | 1.4               | 0.489†   |
significant differences between the groups during the study period. Regarding the data on the body composition evaluated using the whole-body DXA, both fat-free mass and SMI were significantly decreased in both groups at 24 weeks (\(p\) values were all <0.001), but no significant differences were observed in these parameters between the groups. As the prescription rate of sulfonylureas significantly differed between the groups (Table 2), further analyses were performed according to the use of sulfonylureas. Changes in either fat-free mass or SMI did not differ between the IT and CT groups, irrespective of the use of sulfonylureas (data not shown). In participants with a BMI less than 25 kg/m\(^2\) at baseline, similar results were observed (changes in limb fat-free mass: \(-0.3 \pm 0.7\) kg and \(-0.3 \pm 0.5\) kg; SMI: \(-0.1 \pm 0.2\) and \(-0.1 \pm 0.2\) in the IT group and the CT group, respectively).

In contrast, fat mass was significantly decreased in both groups (\(-2.0\) kg in the IT group, \(p < 0.001\) and \(-1.4\) kg in the CT group, \(p < 0.001\)). Interestingly, trunk fat (abdominal fat accumulation) was more decreased in participants in the IT group (\(-1.5\) kg) than those in the CT group (\(-0.9\) kg), and the between-group difference in these fat parameters reached statistical significance (\(-0.5\) kg [95% confidence interval \(-0.9\) to \(-0.1\)]). The reduction of trunk fat mass in each group was almost comparable between participants with a low BMI (<25 kg/m\(^2\)) and those with a high BMI (\(\geq 25\) kg/m\(^2\)); \(-1.5\) kg and \(-1.5\) kg in the IT group and \(-0.8\) kg and \(-1.0\) kg in the CT group, respectively.

### Changes in metabolic profiles

Table 5 shows changes in glucose and lipid metabolism, blood pressure, transaminases, kidney function, and uric acid levels. Fasting plasma glucose and HbA1c levels were significantly decreased by approximately 1.5 mmol/L and 0.5%, respectively, in both groups (\(p\) values for fasting plasma glucose and HbA1c levels at 4, 8, 12, and 24 weeks versus at baseline values were all <0.001), but the changes were comparable between the groups at each time point. Participants in the IT group were more vulnerable to a gradual decline in systolic blood pressure than those in the CT group, but the between-group difference did not attain statistical significance during the study period. No significant between-group differences were observed in lipid metabolism, liver enzymes, kidney function, and uric acid throughout the study. Table 6 shows changes in adipokines and cytokines during the study. Adiponectin levels were significantly increased in both groups (\(p < 0.001\) in the IT group and \(p = 0.011\) in the CT group), however; no significant difference was observed in the group comparison (0.7 [95% CI: 0.1–1.6] in the IT group vs. 0.4 [95% CI: –0.4–1.2] in the CT group, \(p = 0.088\)). Leptin levels were significantly decreased in the IT group (\(p = 0.023\)) but not in the CT group (\(p = 0.386\)). Adipokines and cytokines other than adiponectin and leptin neither differed at baseline nor changed from baseline to 24 weeks in both groups.

### Table 2 Cont.

|                      | IT group \((N = 72)\) | CT group \((N = 69)\) | \(p\) values |
|----------------------|-----------------------|-----------------------|--------------|
| Beta blockers (%)    | 4.2                   | 8.7                   | 0.319 \(\dagger\) |
| Diuretics (%)        | 4.2                   | 7.2                   | 0.487 \(\dagger\) |
| MRAs (%)             | 0.0                   | 1.4                   | 0.489 \(\dagger\) |
| Statins (%)          | 40.3                  | 44.9                  | 0.577 \(\dagger\) |
| Fibrates (%)         | 2.8                   | 4.3                   | 0.676 \(\dagger\) |
| Ezetimib (%)         | 4.2                   | 0.0                   | 0.245 \(\dagger\) |
| EPAs (%)             | 11.1                  | 13.0                  | 0.725 \(\dagger\) |
| UA lowering agents (%) | 4.2                  | 5.8                   | 0.715 \(\dagger\) |
| Antiplatelet agents (%) | 19.4                 | 13.0                  | 0.304 \(\dagger\) |
| Anticoagulants (%)   | 4.2                   | 4.3                   | 1.000 \(\dagger\) |

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ALT, alanine transaminase; ARBs, angiotensin receptor blockers; AST, aspartate aminotransferase; CCBs, calcium channel blockers; DPP4, dipeptidyl peptidase 4; EPA, eicosapentaenoic acid; GIs, glycosidase inhibitors; GLP1-RA, glucagon-like peptide-1 receptors agonist; GTP, glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MRA, mineralocorticoid receptor agonist; TZDs, thiazolidinediones; UA, uric acid.

\(\dagger\) Chi-square test or Fisher’s exact test
Association between adherence to the resistance training and changes in body composition

As shown in Fig. 3, adherence to the resistance training did not affect the changes in parameters of non-fat body composition, including limb fat-free mass, whereas a higher adherence rate to the resistance training was significantly associated with the reduction of body fat.

Correlation of change in physical activities with changes in metabolic profiles

As shown in Table 7, there were no significant correlations between physical intensity and metabolic profiles. However, the achievement rate of resistance training tended to correlate with the changes in HbA1c and hsCRP levels. In the study population as a whole, no significant correlation of step counts with metabolic profiles, other than HDL cholesterol ($r = 0.158, p = 0.073$), was observed (data not shown).

Safety

Although a recent meta-analysis of trials using canagliflozin, DAPA, and empagliflozin and real-world data in the comparison between canagliflozin and glucagon-like peptide-1 receptor agonists did not support a harmful effect of SGLT2 inhibitors on bone [26, 27], special attention should be paid to participants in this study who were encouraged to maintain the protocol for intensive exercise. No severe adverse events, including admission due to musculoskeletal disorders, were reported in either group. However, two participants in the IT group (2.8%) suffered a bone fracture (one of the sacral bone and one of the humerus). Other than bone fractures, six (8.3%) patients in the IT group and two (2.9%) in the CT group experienced musculoskeletal disorders. Adverse effects associated with SGLT2 inhibitors may include genitourinary tract infections and, rarely, euglycemic diabetic ketoacidosis [28]. Genitourinary tract infection was reported in 4 (5.6%) and 7 (10.1%) participants in the IT and CT groups, respectively. Diabetic ketoacidosis was not observed in either groups. One participant in each group experienced mild hypoglycemia.

Discussion

In this study, we demonstrated that the administration of SGLT2 inhibitor DAPA significantly reduced HbA1c

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Table 3  Step counts, physical activities of moderate or higher intensity (≥3.0 Mets) and total amount of resistance training during the study period

|                      | IT group |               | CT group |               | p values |
|----------------------|----------|---------------|----------|---------------|----------|
|                      | Median (IQR) | Achievement rate (%) | Median (IQR) | Achievement rate (%) |          |
| Steps                |          |               |          |               |          |
| Whole period         | 8,747 (5,959–10,504) | 56 | 6,854 (559–8,573) | 64 | 0.006 |
| Baseline–12 week     | 8,970 (6,617–10,799) | 57 | 6,864 (5,599–8,793) | 68 | 0.003 |
| 12 weeks–24 weeks    | 8,644 (5,678–10,286) | 51 | 6,491 (4,764–8,810) | 55 | 0.030 |
| Activity time        |          |               |          |               |          |
| (Mets ≥3.0) (min/day)|          |               |          |               |          |
| Whole period         | 20.9 (11.1–35.6) | 31 | 15.6 (8.5–27.3) | 19 | 0.038 |
| Baseline–12 week     | 22.4 (11.4–36.3) | 29 | 15.9 (8.7–26.0) | 19 | 0.032 |
| 12 weeks–24 weeks    | 19.4 (9.4–36.3) | 29 | 14.5 (7.2–26.1) | 13 | 0.033 |
| Total amount of      |          |               |          |               |          |
| resistance training  |          |               |          |               |          |
|※ Average of total    |          |               |          |               |          |
| amount of resistance  |          |               |          |               |          |
| training (times X    |          |               |          |               |          |
| sets X items)        |          |               |          |               |          |
| Whole period         | 142 (91–173) | 63.9 | N/A       | N/A          |          |
| Baseline–4 weeks     | 158 (118–176) | 77.8 | N/A       | N/A          |          |
| 4 weeks–8 weeks      | 159 (120–179) | 79.2 | N/A       | N/A          |          |
| 8 weeks–12 weeks     | 150 (99–180) | 70.8 | N/A       | N/A          |          |
| 12 weeks–16 weeks    | 146 (96–174) | 68.1 | N/A       | N/A          |          |
| 16 weeks–20 weeks    | 135 (81–179) | 58.3 | N/A       | N/A          |          |
| 20 weeks–24 weeks    | 131 (76–179) | 51.4 | N/A       | N/A          |          |

※ Average of total amount of resistance training (times X sets X items). 180 means that participants completed all training during the period.

† Steps; ≥8,000 in IT and ≥6,000 in CT, Activity time (Mets ≥3.0); ≥30 min, Total amount of resistance training; ≥108
### Table 4  Changes in body composition

|                          | IT group \((N=72)\) | CT group \((N=69)\) | IT group | CT group | LS mean difference \(95\% \text{ CI}\) | \(p\) values |
|--------------------------|----------------------|----------------------|----------|----------|------------------------------------------|-------------|
| **Weight (kg)**          |                      |                      |          |          |                                          |             |
| Baseline                 | 69.8 ± 12.9          | 68.8 ± 13.0          |          |          |                                          |             |
| 4 weeks                  | 69.1 ± 12.8          | 68.1 ± 12.8          | -0.7 ± 1.2 | -0.8 ± 1.3 | 0.670                                    |             |
| 8 weeks                  | 68.6 ± 12.8          | 67.1 ± 12.5          | -1.3 ± 1.4 | -1.3 ± 1.7 | 0.885                                    |             |
| 12 weeks                 | 68.2 ± 12.5          | 67.0 ± 12.6          | -1.6 ± 1.7 | -1.4 ± 1.7 | 0.431                                    |             |
| 24 weeks                 | 67.4 ± 13.2          | 66.1 ± 12.9          | -2.7 ± 2.3 | -2.2 ± 1.9 | 0.190                                    |             |
| **BMI (kg/m\(^2\))**    |                      |                      |          |          |                                          |             |
| Baseline                 | 25.7 ± 3.5           | 25.5 ± 4.0           |          |          |                                          |             |
| 4 weeks                  | 25.5 ± 3.5           | 25.2 ± 4.0           | -0.25 ± 0.43 | -0.30 ± 0.48 | 0.535                                    |             |
| 8 weeks                  | 25.3 ± 3.4           | 24.9 ± 4.0           | -0.47 ± 0.51 | -0.48 ± 0.63 | 0.898                                    |             |
| 12 weeks                 | 25.2 ± 3.4           | 24.9 ± 3.9           | -0.58 ± 0.61 | -0.53 ± 0.61 | 0.607                                    |             |
| 24 weeks                 | 24.8 ± 3.6           | 24.6 ± 4.0           | -1.00 ± 0.84 | -0.80 ± 0.69 | 0.246                                    |             |
| **Fat-free mass (kg)**   |                      |                      |          |          |                                          |             |
| Baseline                 | 47.2 ± 8.9           | 46.8 ± 9.4           |          |          |                                          |             |
| 24 weeks                 | 46.7 ± 8.8           | 45.7 ± 9.4           | -0.6 ± 1.5 | -0.5 ± 1.2 | -0.1 (-0.5 – 0.4)                       | 0.830       |
| **Fat mass (kg)**        |                      |                      |          |          |                                          |             |
| Baseline                 | 21.1 ± 7.4           | 20.3 ± 8.4           |          |          |                                          |             |
| 24 weeks                 | 19.2 ± 7.7           | 19.0 ± 8.0           | -2.0 ± 1.8 | -1.4 ± 1.7 | -1.1 (-1.1 – 0.1)                       | 0.096       |
| **Limb fat-free mass (kg)** |            |                      |          |          |                                          |             |
| Baseline                 | 20.1 ± 4.6           | 19.9 ± 4.6           |          |          |                                          |             |
| 24 weeks                 | 19.9 ± 4.6           | 19.4 ± 4.8           | -0.3 ± 0.9 | -0.2 ± 0.9 | -0.2 (-0.4 – 0.1)                       | 0.249       |
| **Limb fat mass (kg)**   |                      |                      |          |          |                                          |             |
| Baseline                 | 7.2 ± 2.6            | 7.2 ± 3.4            |          |          |                                          |             |
| 24 weeks                 | 6.8 ± 2.8            | 6.7 ± 3.2            | -0.5 ± 0.7 | -0.5 ± 0.6 | 0.0 (-0.2 – 0.2)                        | 0.926       |
| **Skeletal muscle index**|                      |                      |          |          |                                          |             |
| Baseline                 | 7.3 ± 1.1            | 7.3 ± 1.2            |          |          |                                          |             |
| 24 weeks                 | 7.3 ± 1.1            | 7.1 ± 1.2            | -0.1 ± 0.3 | -0.1 ± 0.3 | -0.1 (-0.2 – 0.1)                       | 0.287       |
| **Trunk fat mass (kg)**  |                      |                      |          |          |                                          |             |
| Baseline                 | 12.9 ± 5.1           | 12.3 ± 5.2           |          |          |                                          |             |
| 24 weeks                 | 11.5 ± 5.1           | 11.5 ± 4.9           | -1.5 ± 1.2 | -0.9 ± 1.2 | -0.5 (-0.9 – 0.1)                       | 0.018       |
| **Android (kg)**         |                      |                      |          |          |                                          |             |
| Baseline                 | 2.5 ± 0.9            | 2.3 ± 1.0            |          |          |                                          |             |
| 24 weeks                 | 2.3 ± 0.9            | 2.1 ± 0.9            | -0.3 ± 0.3 | -0.2 ± 0.2 | -0.1 (-0.2 – 0.0)                       | 0.028       |
| **Gynoid (kg)**          |                      |                      |          |          |                                          |             |
| Baseline                 | 3.2 ± 1.0            | 3.1 ± 1.2            |          |          |                                          |             |
| 24 weeks                 | 2.9 ± 1.1            | 2.9 ± 1.2            | -0.3 ± 0.2 | -0.2 ± 0.2 | -0.1 (-0.2 – 0.0)                       | 0.017       |

Android and gynoid were measured in 52 in the IT group and 52 in the CT group.
Table 5  Changes in metabolic profiles

|                         | Baseline | 4 weeks | 8 weeks | 12 weeks | 24 weeks |
|-------------------------|----------|---------|---------|----------|----------|
| **HbA1c (%)**           |          |         |         |          |          |
| IT group                | 7.7 ± 0.8| 7.4 ± 0.8| 7.2 ± 0.7| 7.2 ± 0.7| 7.2 ± 0.7|
| CT group                | 7.7 ± 0.8| 7.4 ± 0.7| 7.2 ± 0.6| 7.1 ± 0.6| 7.2 ± 0.6|
| *p* value for group comparison | 0.720    | 0.595   | 0.880   | 0.987    | 0.785    |
| **Glucose (mmol/L)**    |          |         |         |          |          |
| IT group                | 8.9 ± 1.7| 7.7 ± 1.4| 7.4 ± 1.3| 7.5 ± 1.4| 7.4 ± 1.3|
| CT group                | 8.8 ± 1.8| 7.9 ± 1.4| 7.6 ± 1.3| 7.5 ± 1.4| 7.6 ± 1.3|
| *p* value for group comparison | 0.957    | 0.580   | 0.668   | 0.855    | 0.579    |
| **Systolic blood pressure (mmHg)** |          |         |         |          |          |
| IT group                | 136 ± 16 | 133 ± 15 | 131 ± 15| 129 ± 17 | 127 ± 15 |
| CT group                | 131 ± 17 | 128 ± 17 | 128 ± 17| 126 ± 16 | 127 ± 16 |
| *p* value for group comparison | 0.066    | 0.799   | 0.589   | 0.286    | 0.227    |
| **Diastolic blood pressure (mmHg)** |          |         |         |          |          |
| IT group                | 81 ± 11  | 79 ± 11  | 78 ± 10 | 77 ± 11  | 78 ± 11  |
| CT group                | 80 ± 11  | 78 ± 11  | 77 ± 12 | 77 ± 11  | 78 ± 10  |
| *p* value for group comparison | 0.553    | 0.935   | 0.999   | 0.236    | 0.477    |
| **Triglycerides (mmol/L)** |          |         |         |          |          |
| IT group                | 1.2 (0.9–2.1)| 1.0 (0.8–1.5)| 1.3 (0.8–1.9)| 1.1 (0.9–1.5)| 1.1 (0.8–1.5) |
| CT group                | 1.5 (1.0–2.1)| 1.2 (0.9–1.7)| 1.3 (0.8–1.9)| 1.2 (0.9–1.6)| 1.2 (0.9–1.7) |
| *p* value for group comparison | 0.244    | 0.972   | 0.756   | 0.564    | 0.548    |
| **HDL cholesterol (mmol/L)** |          |         |         |          |          |
| IT group                | 1.5 ± 0.4| 1.5 ± 0.4| 1.5 ± 0.4| 1.5 ± 0.4| 1.6 ± 0.4|
| CT group                | 1.4 ± 0.3| 1.4 ± 0.3| 1.5 ± 0.4| 1.5 ± 0.3| 1.5 ± 0.4|
| *p* value for group comparison | 0.498    | 0.670   | 0.849   | 0.978    | 0.478    |
| **LDL cholesterol (mmol/L)** |          |         |         |          |          |
| IT group                | 3.0 ± 0.9| 2.9 ± 0.9| 3.0 ± 0.9| 2.9 ± 1.0| 2.9 ± 0.9|
| CT group                | 3.1 ± 0.8| 3.0 ± 0.7| 3.1 ± 0.8| 3.0 ± 0.7| 2.9 ± 0.7|
| *p* value for group comparison | 0.754    | 0.259   | 0.397   | 0.343    | 0.196    |
| **AST (U/L)**           |          |         |         |          |          |
| IT group                | 21 (18–28)| 23 (18–30)| 22 (18–29)| 22 (17–29)| 21 (17–26) |
| CT group                | 22 (19–28)| 24 (19–30)| 21 (18–29)| 23 (18–29)| 22 (18–25) |
| *p* value for group comparison | 0.511    | 0.968   | 0.622   | 0.439    | 0.844    |
| **ALT (U/L)**           |          |         |         |          |          |
| IT group                | 25 (17–38)| 24 (17–36)| 22 (16–34)| 22 (16–35)| 21 (17–26) |
| CT group                | 26 (15–45)| 26 (16–41)| 23 (16–36)| 22 (16–36)| 23 (16–37) |
| *p* value for group comparison | 0.460    | 0.952   | 0.898   | 0.792    | 0.472    |
| **γ-GTP (U/L)**         |          |         |         |          |          |
| IT group                | 33 (23–51)| 28 (19–43)| 28 (20–38)| 26 (18–40)| 27 (19–45) |
| CT group                | 38 (26–52)| 32 (23–46)| 29 (21–41)| 27 (21–41)| 31 (21–42) |
| *p* value for group comparison | 0.453    | 0.861   | 0.666   | 0.998    | 0.510    |
levels, weight, and BMI. Regarding the body composition, no significant differences in the changes in either fat-free mass or SMI were observed between participants with DAPA and intensive exercise and those with DAPA alone. In contrast, intensive exercise, especially resistance training, significantly reduced body fat accumulation, including trunk fat, which is considered an indicator of abdominal obesity following initiation of SGLT2 inhibitor treatment.

Our concern that SGLT2 inhibitors could reduce fat-free mass was based on the findings from recent human studies [16-20]. On the other hand, DAPA and canagliflozin have been reported to reduce fat mass without a significant change in fat-free mass in patients with type 2 diabetes [29-32]. Although reasons for this discrepancy are unclear, a recent elegant study in a diabetic animal model (Akita mice) revealed that normalization of blood glucose by an SGLT2 inhibitor (empagliflozin) without

Table 5  Cont.

|                           | Baseline | 4 weeks   | 8 weeks   | 12 weeks  | 24 weeks  |
|---------------------------|----------|-----------|-----------|-----------|-----------|
| **eGFR (mL/min/1.73 m²)** |          |           |           |           |           |
| IT group                  | 82.4 ± 15.8 | 77.9 ± 15.7 | 78.5 ± 14.7 | 79.9 ± 15.5 | 79.7 ± 16.0 |
| CT group                  | 82.0 ± 17.9 | 79.0 ± 18.5 | 80.8 ± 20.0 | 82.2 ± 19.7 | 81.2 ± 18.0 |
| p value for group comparison | 0.879    | 0.332     | 0.101     | 0.106     | 0.636     |
| **Uric acid (μmol/L)**   |          |           |           |           |           |
| IT group                  | 312 ± 69  | 282 ± 69  | 281 ± 65  | 280 ± 73  | 289 ± 75  |
| CT group                  | 326 ± 73  | 286 ± 74  | 290 ± 77  | 290 ± 73  | 297 ± 73  |
| p value for group comparison | 0.236    | 0.261     | 0.813     | 0.834     | 0.710     |
| **Urinary ACR (mg/g)**   |          |           |           |           |           |
| IT group                  | 15 (8–45) | 14 (7–33) | 12 (7–28) |           |           |
| CT group                  | 21 (7–52) | 16 (6–71) | 17 (6–71) |           |           |
| p value for group comparison | 0.980    | 0.367     | 0.479     |           |           |

Table 6  Changes in adipokines and cytokines levels

|                           | Changes from baseline | p values |
|---------------------------|-----------------------|----------|
| **Adiponectin (μg/mL)**   | IT group              | CT group | IT group | CT group |
| Baseline                  | 6.4 (4.8–8.6)         | 7.2 (4.7–9.8) | 0.7 (0.1–1.6) | 0.4 (–0.4–1.2) | 0.088 |
| 24 weeks                  | 7.2 (5.6–10.3)        | 7.1 (5.1–10.6) | 0.2 (–0.3–0.5) | 0.1 (–0.2–0.5) | 0.707 |
| **Leptin (ng/mL)**        |                       |          |          |          |          |
| Baseline                  | 11.7 (7.8–19.2)       | 12.3 (7.1–17.5) | –0.7 (–3.0–1.2) | –0.6 (–1.9–1.7) | 0.331 |
| 24 weeks                  | 10.4 (6.7–15.5)       | 11.4 (7.3–17.5) | –0.3 (–0.9–0.6) | –0.6 (–1.9–1.7) | 0.331 |
| **Interleukin 6 (pg/mL)** |                       |          |          |          |          |
| Baseline                  | 1.7 (1.2–2.2)         | 1.4 (1.0–2.1) | 0.2 (–0.3–0.5) | 0.1 (–0.2–0.5) | 0.707 |
| 24 weeks                  | 1.6 (1.1–2.2)         | 1.4 (1.1–2.2) | 0.2 (–0.3–0.5) | 0.1 (–0.2–0.5) | 0.707 |
| **High-sensitivity TNFα (pg/mL)** |               |          |          |          |          |
| Baseline                  | 0.54 (0.46–0.69)      | 0.54 (0.43–0.64) | –0.01 (–0.08–0.07) | –0.01 (–0.11–0.06) | 0.774 |
| 24 weeks                  | 0.52 (0.42–0.67)      | 0.52 (0.43–0.60) | –0.01 (–0.08–0.07) | –0.01 (–0.11–0.06) | 0.774 |
| **High-sensitivity CRP (mg/dL)** |           |          |          |          |          |
| Baseline                  | 0.6 (0.3–1.4)         | 0.7 (0.3–1.3) | 0.0 (–0.4–0.1) | –0.1 (0.3–0.2) | 0.720 |
| 24 weeks                  | 0.5 (0.3–1.0)         | 0.6 (0.3–1.3) | 0.0 (–0.4–0.1) | –0.1 (0.3–0.2) | 0.720 |

Abbreviations: CRP, C-reactive protein; TNF, tumor necrosis factor.
affecting insulin secretion could prevent the reduction in skeletal muscle mass and muscle fiber area apparent in the control Akita mice, and the increased expression of muscle atrophy-related genes was also attenuated by the drug [33]. In most participants in our study, an improvement of glycemic control was observed by the administration of DAPA. Give these results, SGLT2 inhibitors may have a low potential for sarcopenia/frailty as long as

Fig. 3 Changes in parameters of the body composition according to adherence to the resistance training. White, gray, and black bars indicate participants with the achievement rate of the resistance training of <60%, ≥60% and <80%, and ≥80%, respectively. Android and gynoid were measured in 52 participants in the IT group and 52 participants in the CT group.

Table 7 Correlation of adherence to intensive exercise with changes in metabolic parameters in the IT group

| Metabolic data            | Physical activities of 3.0 Mets or more (min/day) | Resistance training (%) |
|---------------------------|--------------------------------------------------|-------------------------|
|                           | $r$      | $p$ values | $r$      | $p$ values |
| HbA1c                     | -0.01    | 0.964      | -0.21    | 0.077      |
| Triglycerides             | 0.08     | 0.544      | -0.02    | 0.845      |
| HDL cholesterol           | 0.07     | 0.600      | 0.06     | 0.626      |
| LDL cholesterol           | 0.18     | 0.149      | 0.11     | 0.384      |
| Systolic blood pressure   | -0.14    | 0.270      | -0.17    | 0.167      |
| Diastolic blood pressure  | -0.07    | 0.550      | -0.11    | 0.355      |
| eGFR                      | 0.06     | 0.657      | -0.16    | 0.178      |
| Urinary ACR               | -0.08    | 0.549      | -0.10    | 0.412      |
| AST                       | 0.03     | 0.812      | 0.02     | 0.889      |
| ALT                       | 0.05     | 0.693      | 0.04     | 0.733      |
| Adiponectin               | 0.03     | 0.833      | 0.11     | 0.377      |
| Leptin                    | -0.01    | 0.967      | -0.13    | 0.317      |
| IL6                       | -0.10    | 0.427      | -0.11    | 0.383      |
| High-sensitivity CRP      | -0.06    | 0.655      | -0.24    | 0.053      |
| High-sensitivity TNF-α    | 0.07     | 0.561      | -0.13    | 0.275      |
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patients can adequately manage glycemic control following SGLT2 inhibitor treatment.

In a previous study reporting significant improvement of muscle strength in patients with type 2 diabetes [25], all subjects attended an exercise laboratory on 3 non-consecutive days per week during the 6-month intervention, and the exercise was supported by trained instructors to achieve the progressive high-intensity resistance training. In our study, participants mainly underwent resistance training at home without any instructor assistance. The method was suitable for practical use at a very low cost, but strict monitoring of resistance training was impossible during the study. Eventually, the high adherence rate to the intensive exercise in participants in the IT group was unable to be maintained during the study period. Therefore, we performed a sensitivity analysis in participants who had a high adherence rate of resistance training throughout the study; however, neither fat-free mass nor SMI was increased by the resistance training. A recent systematic review and meta-analysis of seven RCTs investigating the effects of exercise on sarcopenia demonstrated that muscle strength and physical performance, such as walking, can be improved in most studies, but only 3/7 RCTs revealed a significant increase in muscle mass [34]. Further studies are necessary to investigate the effect of intensive exercise with SGLT2 inhibitors on muscle strength and physical performance in patients with type 2 diabetes. Dietary intervention, in addition to exercise, may also be effective in increasing muscle mass and quality. Rondanelli et al. reported that intensive exercise with a modification of diet, including whey protein, amino acids, and vitamin D supplementation, could increase fat-free mass and muscle strength and functionality in sarcopenic elderly people [35]. Given these findings, stricter monitoring of exercise, technical support by trained instructors, and dietary intervention may be considered to preserve muscle mass and function in patients with type 2 diabetes.

Other than the effects of exercise with SGLT2 inhibitors on muscle, we observed several favorable impacts of exercise on the metabolic profiles and body fat composition of the study participants. Step counts were correlated with changes in HDL cholesterol levels with a marginal significance. Participants with a higher adherence to the resistance training showed a significantly reduced fat mass (Fig. 3) and tended to reduce their HbAlc and hsCRP levels (Table 7). Furthermore, serum adiponectin levels were also increased by the intensive exercise (Table 6). Although patients with good adherence to the intensive exercise may have high adherence of both DAPA and diet, these data suggest that intensive exercise after administration of SGLT2 inhibitors can reduce abdominal fat accumulation more effectively than SGLT2 inhibitors alone, presumably leading to improvements of both glycemic control (insulin resistance) and chronic micro-inflammation.

There were some limitations to our study. Firstly, our study had a relatively small sample size and a short follow-up period. Therefore, the generalization of our findings may be limited. Secondly, the adherence to the intensive exercise was not high during the study period, presumably affecting the analysis of the primary endpoint. Thirdly, a dietary assessment was not performed during the study. Fourthly, three different equipment of the whole body DXA were used in this study, however, between Lunar iDXA system and Prodigy DXA system, estimation differences in either fat-free mass or fat mass including trunk fat were not reported [36]. Regional fat and fat-free mass were reported to be highly correlated between Lunar iDXA system and Discovery DXA system [37]. In addition, body composition was evaluated using the same equipment for each patient. Thus, the change in the body composition was thought to be reliable. Fifthly, we were unable to evaluate extracellular water. Reduction of fat-free mass could be explained, at least in part, by reduction in extracellular water. Reduction in excess body water has been demonstrated following treatment with SGLT2 inhibitors but not by exercise. Sixthly, the group treated with intensive exercise without administration of SGLT2 inhibitors was not incorporated in this study. Finally, we were unable to obtain information regarding muscle strength, such as handgrip power. Further studies are needed to evaluate whether intensive exercise can prevent the progression of sarcopenia/frail after administration of SGLT2i inhibitors in patients with type 2 diabetes.

In conclusion, this study demonstrates that intensive exercise, which is practicable without any assistance of an instructor, do not prevent the reduction of fat-free mass after administration of SGLT2 inhibitors but can more reduce abdominal fat accumulation than SGLT2 inhibitors alone, presumably leading to improvements of hyperglycemia and chronic inflammation in patients with type 2 diabetes.

Contributors

All authors contributed significantly. R.B., N.S., J.I., Ya.O., T.F., and T.T. researched data. R.B. performed the statistical analyses. R.B. wrote the manuscript. R.B., N.S., J.I., Ya.O., T.F., J.K., T.Y, and Yo.O. contributed to intellectual discussion and reviewed and edited the manuscript. R.B. was the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the
accuracy of the data analysis. All authors reviewed and approved the final manuscript.

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Disclosure

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