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ORIGINAL ARTICLE

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Double-blinded, randomized, and controlled study on the effects of canagliflozin after bariatric surgery: A pilot study

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Summary

Setting: Bariatric surgery is indicated for patients diagnosed with obesity and type 2 diabetes. Many patients achieve type 2 diabetes remission soon after bariatric surgery. Even though most maintain good glycemic control, remission is not maintained in all patients, and as a result, some patients may relapse. Type 2 diabetes relapse is common in patients who regain weight; weight regain is prevalent 1 to 2 years after surgery. Additional pharmacotherapy may be required to aid bariatric surgery in fostering weight loss and reducing blood glucose levels.

Objectives: The purpose of this clinical trial was to determine the effects of canagliflozin in participants who initially achieved type 2 diabetes remission but subsequently relapsed.

Methods: The double-blinded, randomized, and prospective study recruited participants (n = 16) roughly 3 years after bariatric surgery. The participants were followed for 6 months.

Results: Body mass index (−1.24 kg/m^2) and body weight (−3.7 kg) were significantly reduced with canagliflozin therapy versus placebo. There were improvements in body fat composition as denoted by reductions in android (−3.00%) and truncal (−2.67%) fat. Also, there were differences in blood glucose and hemoglobin A1C at 6 months.

Conclusion: After bariatric surgery, canagliflozin improved weight loss and glycemic outcomes in participants with type 2 diabetes. Canagliflozin also facilitated improvements in body fat composition.

KEYWORDS

bariatric surgery, body composition, canagliflozin, type 2 diabetes

1 | INTRODUCTION

While lifestyle modification remains a staple in the therapeutic management of patients with new onset type 2 diabetes (T2D),[1] more aggressive therapies are needed to treat patients with severe obesity and long-standing T2D. Bariatric surgery is the preeminent therapeutic option for patients who have poorly controlled T2D and who have class 2 or 3 obesity.[2] Not only does bariatric surgery facilitate euglycemia and weight loss in the short term,[3] but all-cause mortality is likely reduced in the long term.[4] Given that the positive effects of bariatric surgery are so profound,[5] its popularity has steadily increased.

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However, while bariatric surgery is effective in fostering weight loss and improving glycaemic control, there are limits to its potential as a stand-alone therapeutic option. Although T2D control within the 2-year window after bariatric surgery is certainly improved relative to presurgery, glycemic control begins to degrade after the 2-year threshold in many patients especially if they had a prolonged duration of diabetes prior to surgery.[2] As such, the patients will require the assistance of adjuvant pharmacotherapy to offset the weight regain and the larger glycaemic fluctuations that they experience. On the higher end of the spectrum, one study suggests that roughly 30% of patients may require additional therapeutic assistance 5 years after bariatric surgery.[6] The majority of the patients are poorly controlled before they undergo bariatric surgery and are clinically diagnosed with T2D for a longer period of time.[7] To date, a paucity of tier 1 evidence exists on viable antidiabetic medications that can be prescribed in synergy with bariatric surgery. Therefore, clinical judgment is exercised when deciding which agent to prescribe. Some studies have been retrospective in nature and, for example, investigated the effects of liraglutide on weight loss outcomes[8-10]; while one study noted the effects of sitagliptin after bariatric surgery, additional insight is needed.[11]

Canagliflozin, a renal sodium-glucose-cotransporter-2 (SGLT2) inhibitor that acts independently of insulin, fosters glycosuria to lower glucose concentrations. Cardiovascular and renal benefits are derived from treatment with canagliflozin in addition to its adjuvant effects: decreases in weight and improvements in glucose control.[12,13] Given that canagliflozin has a mechanism of action that is complementary to bariatric surgery, it is a suitable agent for patients who underwent bariatric surgery. The purpose of this clinical trial was to investigate the effects of canagliflozin in participants who underwent bariatric surgery. In relation to placebo, the hypothesis was that canagliflozin, an agent that acts independently of insulin, would foster more substantial reductions in weight and blood glucose. In turn, it was postulated that the secondary outcome variables would improve: C-reactive protein and adiponectin. The pilot study was the first to characterize the effects of canagliflozin on clinical and bariatric parameters in participants who had recurrent T2D and who underwent bariatric surgery.

2 | MATERIALS AND METHODS

An outline of the protocol was published previously,[14] but the methods written herein were updated to reflect the changes to the protocol. The clinical trial is registered in clinicaltrials.gov (NCT02912455). The protocol was approved by the institutional review board. Participants received $25 per visit.

Participants who underwent bariatric surgery >1 but <15 years prior to the screening visit were eligible. Furthermore, the age restriction was between 20 to 75 years. Originally, 65 years of age was the upper limit for the study. To be eligible, participants must have undergone adjustable gastric banding, Roux-en-Y gastric bypass, or sleeve gastrectomy. A T2D diagnosis was required before and after bariatric surgery. Participants must of had an hemoglobin A1C (A1C) $\geq$ 6.5% but $\leq$11% at randomization. At the outset, the lower limit for the A1C was 7.5%. The ranges for age and A1C were broadened to increase enrolment. An estimated glomerular filtration rate of ≥60 mL/min prior to randomization was required.

The exclusion criteria included a diagnosis of type 1 diabetes, other bariatric surgical procedures not outlined in the inclusion criteria, nonresearch-related insulin use, renal failure, cardiomyopathy, and severe depression. Participants with active cancer were also excluded. Inclusion and exclusion criteria were verified upon the review of the patient's medical diagnoses and when the patient was asked about their medical history at the screening visit.

Participants were randomly allocated into a placebo or a canagliflozin group in a 1:2 ratio. If the participants were taking any antidiabetic agents, they were washed out for 8 weeks prior to the randomization visit. As indicated in Figure 1, there were six visits. Participants were asked to fast prior to each visit. During the baseline visit, the participants met with the registered dietician for 45 minutes; no additional visits with the dietician were scheduled after the baseline visit. The dietician visit was instituted for educational purposes. Participants received placebo or canagliflozin at randomization and were followed for the subsequent 6 months.

Immediately prior to breakfast, lunch, and dinner, participants were asked to monitor their blood glucose levels via a glucometer and/or in a diary. The participants did not monitor their daily physical activity or food intake. Hyperglycaemic and hypoglycaemic events were recorded once the participants came in for their visits. For nondiet-controlled participants, moderate hyperglycaemia (>250 mg/dL) was managed with rescue sliding-scale insulin. If their blood glucose was between 251 and 300 mg/dL, 301 and 350 mg/dL, or 351 and 400 mg/dL, they were instructed to inject 6, 8, or 10 units of insulin, respectively. For safety reasons, if a participant was noted to be severely hyperglycaemic (A1C $\geq$ 11%), they were placed on a basal-bolus insulin regimen. The dose was determined by body weight; half the dose was given as long-acting insulin, while the remaining was given as short-acting insulin. Insulin was not provided by the study during the first year of the study as it was considered standard of care. The participants were instructed to document when they used sliding-scale insulin.

Height and weight were measured on a wall-mounted stadiometer and digital scale, respectively. Clinical parameters were collected at randomization, 3, and 6 months. A point-of-care A1C and a complete metabolic panel, which included a fasting glucose measurement, were performed at the three visits. Furthermore, lipid panels and adipokines (adiponectin and leptin) were drawn at randomization and 6 months. Dual-energy X-ray absorptiometry (DEXA) was done at randomization and 6 months to assess body composition and bone mineral density (BMD).

At randomization, participants received 100 mg/day for 2 weeks and then were titrated up to 300 mg/day. As determined by the principal investigator, the participant was maintained on the lower dose if they experienced multiple adverse events. If the symptoms subsided,

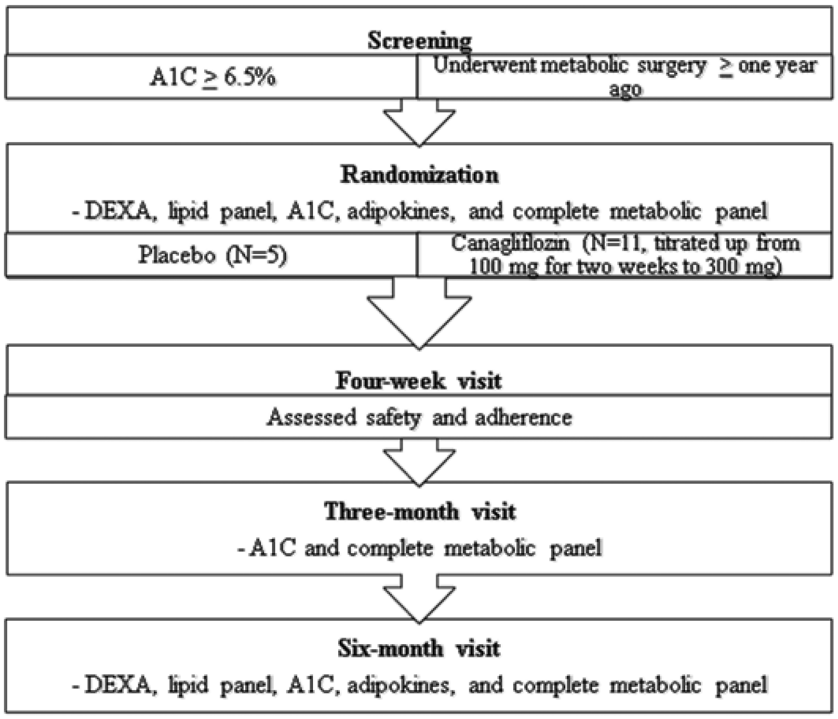

FIGURE 1 Visit outline for participants enrolled in the study. Dual-energy X-ray absorptiometry (DEXA). Hemoglobin A1C (A1C)

they were titrated to the upper dose at their next visit. Participants were instructed to ingest the medication before their first meal of the day.

Medication adherence was assessed by counting the number of medications returned. Therefore, if a participant was given 40 capsules over the next 30 days and returned 10 capsules after that time period, then adherence was 100%. Adherence could not be computed in participant who did not return any medications. All the dispensed capsules were identical in appearance. All participants signed a consent document prior to participating in the study.

3 | STATISTICAL ANALYSIS

Enrolment of 36 participants was planned based on power calculations. Assuming an alpha of.05 and a standard deviation of 0.9% (two-sided *t* test), there was 80% power to detect mean differences of 1.0% in A1C change between the canagliflozin (n = 22) and placebo groups (n = 11). Even if 10% of the participants dropped out, there would still have been sufficient power to detect group differences. By using SAS, a randomization table was generated by the statistician. A strategy of concealed assignment of medication was employed.

Intent-to-treat analysis and per-protocol analyses were conducted. Analysis of covariance models was fit with change as the outcome and group and baseline measures as predictors. For non-normal distributions, the Yuen method and the percentile bootstrap were used because the baseline measures were not covariates.[15] Explanatory effect size delineated whether the differences were small, medium, or large (≥.50).[16] Mean changes with 95% confidence intervals are presented for each group and for the difference at 6 months.

As a sensitivity analysis, the comparison of actual changes was repeated using linear mixed effect models, using maximum likelihood estimation.[17] This has been shown to account for missing data under the assumption that the data are missing at random. In these models, an autoregressive correlation structure within participant was assumed, except for lab values where a variance component error structure was assumed because of poor convergence with more complicated correlation structures. In all models, separate group variances were allowed. Analysis was performed using SAS software (version 9.4; Cary, North Carolina) and R-studio (version 3.3.1).

4 | RESULTS

Table 1 denotes the baseline characteristics of the cohort after the 8-week washout. In the canagliflozin group, the longitudinal reductions in blood glucose and body mass index (BMI) were significant; also, there were longitudinal improvements in body composition as noted by reductions in android adiposity and truncal fat (Table 2). Although participants taking canagliflozin achieved weight loss, lean mass was preserved (54.0 kg at baseline vs 54.4 kg at 6 months).

At 6 months, changes in uric acid levels were significantly different between groups (Table 2). Furthermore, changes in A1C, blood glucose, weight, BMI, percent body fat, percent truncal fat, and percent android fat were significantly different.

After the insulin-administering participant was removed from the analysis (per-protocol), changes in A1C and blood glucose at 6 months remained significant (Table 3). The noted effect sizes were large. Similarly, Table 4 reports the changes in uric acid, BMI, and body composition.

TABLE 1 Baseline demographics and biochemical characteristics after the 8-week washout

	Overall (N = 16)		Placebo (N = 5)		Canagliflozin (N = 11)	
Factor	**N**	**Statistics**	**n**	**Statistics**	**n**	**Statistics**
Age (y)	16	54.0 (34.0, 75.0)	5	44.0 (34.0, 59.0)	11	58.0 (38.0, 75.0)
Male		5 (31.3)		1 (20.0)		4 (36.4)
Female		11 (68.8)		4 (80.0)		7 (63.6)
Height (m)	16	1.7 (1.5, 1.9)	5	1.7 (1.6, 1.9)	11	1.7 (1.5, 1.7)
BMI (kg/m2)	16	39.2 (28.6, 49.4)	5	37.9 (31.9, 44.7)	11	39.6 (28.6, 49.4)
Weight (kg)	16	108.9 (78.3, 133.7)	5	117.5 (86.0, 133.7)	11	108.6 (78.3, 132.9)
Hemoglobin A1c (%)	16	7.4 (6.5, 10.0)	5	8.2 (6.9, 10.0)	11	7.2 (6.5, 8.3)
Fasting glucose (mg/dL)	16	163.5 (105.0, 239.0)	5	164.0 (116.0, 239.0)	11	163.0 (105.0, 204.0)
Diastolic blood pressure (mmHg)	16	76.5 (51.0, 87.0)	5	77.0 (51.0, 86.0)	11	73.0 (52.0, 87.0)
Systolic blood pressure (mmHg)	16	134.5 (106.0, 148.0)	5	133.0 (117.0, 141.0)	11	137.0 (106.0, 148.0)
Uric acid (mg/dL)	16	4.3 (2.9, 7.9)	5	3.9 (3.3, 5.1)	11	4.9 (2.9, 7.9)
Total cholesterol (mg/dL)	16	162.0 (112.0, 257.0)	5	167.0 (135.0, 202.0)	11	160.0 (112.0, 257.0)
Triglycerides (mg/dL)	16	109.5 (59.0, 224.0)	5	107.0 (62.0, 121.0)	11	130.0 (59.0, 224.0)
LDL (mg/dL)	16	92.0 (31.0, 175.0)	5	108.0 (67.0, 120.0)	11	87.0 (31.0, 175.0)
HDL (mg/dL)	16	49.0 (28.0, 81.0)	5	51.0 (29.0, 60.0)	11	47.0 (28.0, 81.0)
Body fat %	16	48.6 (29.4, 55.3)	5	44.1 (29.4, 51.0)	11	49.3 (30.5, 55.3)
Lean mass %	16	51.5 (44.7, 70.6)	5	55.9 (49.0, 70.6)	11	50.7 (44.7, 69.5)
Percent truncal fat	16	50.9 (34.9, 55.3)	5	47.8 (34.9, 54.0)	11	53.5 (36.8, 55.3)
Percent android fat	16	53.9 (38.0, 58.6)	5	51.3 (38.0, 56.3)	11	55.6 (41.1, 58.6)
Percent gynoid fat	16	47.7 (27.5, 55.6)	5	47.3 (30.1, 55.6)	11	48.1 (27.5, 55.3)
Spine BMD (g/cm^2)	16	1.2 (1.03, 1.8)	5	1.3 (1.05, 1.3)	11	1.2 (1.03, 1.8)
Leg BMD (g/cm^2)	16	1.2 (1.05, 1.9)	5	1.2 (1.05, 1.4)	11	1.2 (1.07, 1.9)
HMW adiponectin (μg/mL)	16	3.1 (8, 10)	5	3.3 (1.6, 7)	11	2.9 (0.8, 10)
Adiponectin (μg/mL)	16	4.6 (1.5, 17)	5	5 (3, 10)	11	4.2 (1.5, 17)
Leptin (ng/mL)	16	28.5 (4.7, 117)	5	29 (4.7, 117)	11	28 (5.3, 87)
CRP (mg/L)	15	3.7 (0.20, 44.5)	4	0.45 (0.20, 3.8)	11	4.1 (1.00, 44.5)

Note. Statistics presented as median (min, max) or N (column %).
Abbreviations: BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoproteins; HMW, high molecular weight; LDL, low-density lipoproteins.

Table 5 denotes the frequency of adverse events. The first row under each factor indicates the number of participants who reported one hyperglycaemic episode (etc). For example, 11 of the participants did not self-report (or via glucometer) any hyperglycaemic episodes.

The participants were considered enrolled once they consented to be in the study. Forty-five participants were screened on-site. Nineteen total participants failed to qualify prior to being randomized. Twenty-six were enrolled, but data were garnered from 16 participants because of premature discontinuation. Participation in the trial was terminated early in 10 participants because they were nonresponsive to phone calls (etc), failed to come in for their visits, or withdrew consent. The 10 participants who were terminated did not receive medication or placebo and therefore did not have any adverse events or any data of relevance to report.

With regard to participants who were randomized, two participants underwent sleeve gastrectomy, while the remaining 14 underwent Roux-en-Y gastric bypass. One participant underwent sleeve gastrectomy in each group, while four underwent Roux-en-Y gastric bypass in the placebo group. In the canagliflozin group, one participant dropped out after 6 weeks, and one participant dropped out after 3 months. In the placebo group, three participants dropped out after 3 months. The patients who did contact us informed us that their blood glucose levels increased and therefore wanted to withdraw consent; otherwise, they were terminated because they were nonresponsive or failed to come in for their visits. The median number of years from the date of bariatric surgery until the screening visit was 3.8 (1.6, 9.6) and 2.7 (1.24, 4.6) for the canagliflozin and placebo groups, respectively.

At the screening visit, one participant was not taking any medication for their T2D because they did not have health insurance. One participant was using metformin and a dipeptidyl peptidase-4 inhibitor. Three participants were diet controlled. The remaining participants were on a monotherapeutic regimen of metformin. The participants were not taking weight loss medications.

TABLE 2 Actual change at 6 months versus baseline (intent-to-treat analysis)

	Canagliflozin		Placebo			
Outcome	Change (95% CI)	*P* Value	Change (95% CI)	*P* Value	Difference (95% CI)	*P* Value
Body mass index (kg/m^2)	−1.24 (−2.12 to −0.36)	.007	1.65 (−0.42 to 3.72)	.11	−2.89 (−5.14 to −0.64)	.014
Weight (kg)	−3.77 (−6.33 to −1.22)	.006	6.33 (−1.50 to 14.16)	.11	−10.10 (−18.34 to −1.87)	.018
A1C (%)	−0.31 (−0.72 to 0.10)	.13	0.11 (−0.71 to 0.93)	.78	−0.75 (−1.4 to −0.22)[a]	.007[a]
Fasting glucose (mg/dL)	−32.90 (−56.02 to −9.79)	.007	11.71 (−41.24 to 64.66)	.65	−55.7 (−87 to −15)[a]	.01[a]
Diastolic blood pressure (mmHg)	−1.18 (−6.62 to 4.26)	.66	2.95 (−13.69 to 19.60)	.72	−4.13 (−21.64 to 13.37)	.63
Systolic blood pressure (mmHg)	4.62 (−7.10 to 16.34)	.42	12.63 (−5.02 to 30.28)	.15	−8.02 (−29.20 to 13.17)	.44
Uric acid (mg/dL)	−0.47 (−1.02 to 0.08)	.083	0.53 (−0.11 to 1.16)	.094	−1.00 (−1.84 to −0.16)	.025
Total cholesterol (mg/dL)	−0.87 (−26.59 to 24.85)	.94	3.69 (−37.53 to 44.92)	.84	−4.57 (−53.15 to 44.02)	.84
Triglycerides (mg/dL)	−22.46 (−65.15 to 20.22)	.26	−15.90 (−33.02 to 1.21)	.065	−6.56 (−52.55 to 39.43)	.75
LDL (mg/dL)	2.33 (−15.54 to 20.20)	.77	0.86 (−36.89 to 38.60)	.96	1.47 (−40.29 to 43.23)	.94
HDL (mg/dL)	3.22 (−1.05 to 7.50)	.12	16.97 (−5.87 to 39.81)	.13	−13.75 (−36.98 to 9.49)	.21
Percent body fat	−1.82 (−3.83 to 0.20)	.072	2.65 (−1.21 to 6.51)	.15	−4.47 (−8.82 to −0.11)	.045
Percent lean mass	1.82 (−0.20 to 3.83)	.072	−2.65 (−6.51 to 1.21)	.15	4.47 (0.11 to 8.82)	.045
Percent truncal fat	−2.67 (−5.19 to −0.16)	.040	2.74 (−0.14 to 5.63)	.060	−5.42 (−9.24 to −1.59)	.011
Percent android fat	−3.00 (−5.67 to −0.32)	.032	3.33 (0.23 to 6.43)	.038	−6.33 (−10.42 to −2.24)	.007
Percent gynoid fat	−1.69 (−3.65 to 0.28)	.084	2.17 (−2.26 to 6.59)	.30	−3.85 (−8.70 to 0.99)	.11
Spine BMD (g/cm^2)	−0.02 (−0.07 to 0.03)	.40	0.14 (−0.11 to 0.40)	.24	−0.16 (−0.42 to 0.10)	.20
Leg BMD (g/cm^2)	0.01 (−0.03 to 0.05)	.66	−0.04 (−0.37 to 0.28)	.76	0.05 (−0.27 to 0.38)	.72
HMW adiponectin (μg/mL)	1.0 (−2.2 to 4.2)	.50	1.8 (−4.6 to 8.3)	.54	−0.8 (−8.1 to 6.4)	.80
Adiponectin (μg/mL)	0.7 (−4.4 to 5.7)	.77	−3.4 (−9.3 to 2.5)	.23	4.0 (−3.7 to 11.8)	.27
Leptin (ng/mL)	−8.1 (−35.1 to 18.9)	.51	−11 (−93.1 to 71.1)	.77	2.9 (−83.5 to 89)	.94
CRP (mg/L)	−5.35 (−13.81 to 3.12)	.19	3.34 (−0.76 to 7.44)	.098	−8.69 (−18.09 to 0.72)	.066

Note. Mixed effect model.

Abbreviations: A1C, hemoglobin A1C; BMD, bone mineral density; CI, confidence interval; CRP, C-reactive protein; HDL, high-density lipoproteins; HMW, high molecular weight; LDL, low-density lipoproteins.

[a]Yuen method.

TABLE 3 Six-month outcomes (per-protocol)

Outcome	T2D Trimmed Mean	Control Trimmed Mean	Difference (95% CI)	*P* Value	Effect Size
Hemoglobin A1c (%)	−0.35	+0.43	−0.78 (−1.3 to −0.2)	.007[a]	0.76
Glucose (mg/dL)	−37	+16	−52.3 (−85.8 to −13.4)	.01[a]	0.66

Abbreviation: CI, confidence interval.
[a]Yuen method.

TABLE 4 Actual changes at 6 months (per-protocol)

	Medication		Placebo			
Outcome	Change (95% CI)	*P* Value	Change (95% CI)	*P* Value	Difference (95% CI)	*P* Value
Body mass index (kg/m^2)	−1.24 (−2.12 to −0.36)	.008	0.21 (−0.52 to 0.94)	.56	−1.45 (−2.59 to −0.30)	.015
Uric acid	−0.47 (−1.03 to 0.09)	.087	0.89 (0.11 to 1.67)	.031	−1.36 (−2.32 to −0.40)	.011
Body fat percentage	−1.82 (−3.87 to 0.24)	.076	−0.17 (−8.67 to 8.33)	.96	−1.65 (−10.40 to 7.09)	.67
Lean mass percentage	1.82 (−0.24 to 3.87)	.076	0.17 (−8.33 to 8.67)	.96	1.65 (−7.09 to 10.40)	.67
Percent truncal fat	−2.67 (−5.24 to −0.11)	.043	0.52 (−6.65 to 7.68)	.87	−3.19 (−10.80 to 4.42)	.36
Percent android fat	−3.00 (−5.73 to −0.27)	.035	−16.24 (−33.28 to 0.80)	.059	13.24 (−4.01 to 30.50)	.11
Percent gynoid fat	−1.69 (−3.69 to 0.32)	.088	−20.61 (−43.15 to 1.94)	.068	18.92 (−3.72 to 41.55)	.090

Note. Mixed effect model.
Abbreviation: CI, confidence interval.

There were no documented incidents of diabetic ketoacidosis. One participant in the placebo group was instructed to use rapid-acting insulin (Humulin) prior to each meal (up to 10 units) because they had uncontrolled T2D (A1C > 11%). The participant injected around 15 to 25 units of insulin per day. Only two participants were supplied with insulin: the lone participant and one participant in the canagliflozin group who did not repot using it.

5 | DISCUSSION

Now, there are more data to substantiate the assertion that a SGLT2 inhibitor can improve weight loss and glycaemic outcomes in participants who underwent bariatric surgery. Additionally, pharmacological aids such as SGLT2 inhibitors can help maintain rather than promote substantial weight loss. There were three pertinent findings: There were reductions in BMI, blood glucose, and body fat percentage; in the intent-to-treat analysis, improvements in body fat composition were reflected by the reductions in android (central) adiposity. Moreover, between-group changes in uric acid levels at 6 months achieved significance. The data highlight that canagliflozin merits some consideration when deciding which agent to prescribe after bariatric surgery.

If weight loss is facilitated via diet and exercise, the homeostatic response is hyperphagia.[18] By contrast, participants who have undergone bariatric surgery have a reduction in hunger and increase in satiety because of the proposed changes to the homeostatic control of the body fat set point.[19] There are, however, interindividual differences in weight loss outcomes; specifically, some patients are resistant to the positive effects of bariatric surgery, and as a result, caloric intake markedly increases.[20] With a progressive increase caloric intake, there may be T2D relapse.

Given that hyperglycaemia recurs after bariatric surgery in some patients, canagliflozin can offset increases in postprandial glucose levels by facilitating glucose excretion via the renal system.[21] As a result, a negative energy balance and weight loss are facilitated. Thus, as was done in the present study (at least >1 year after surgery), canagliflozin may be prescribed long term after bariatric surgery in participants who were inadequately controlled by their traditional regimen.

As presented in the results, the average weight loss that a patient can expect is around 3.7 kg (Table 2). The results corroborated the noted findings in the literature because weight loss outcomes were similar to that observed in other clinical trials that prescribed canagliflozin (approximately 3 kg).[21]

Few studies have investigated the effects of antidiabetic medications in participants who underwent bariatric surgery. Except for two studies, the remaining were retrospective-based studies. Although there was a discrepancy in the time points (6 months in the present study vs 2 years in the liraglutide study), weight loss outcomes paralleled that of liraglutide in a retrospective study that investigated its effects in a similar population.[9] However, another retrospective study found that patients who were prescribed a high dose of liraglutide (3.0 mg) experienced significant weight loss (−4.7 kg/m^2) after 28 weeks.[22] In comparison, the present study noted reductions of about 1.24 kg/m^2 after roughly 26 weeks. The marked weight loss results achieved by the participants in the liraglutide study were likely confounded by diet, as the participants were instructed to achieve a

TABLE 5 Medication adherence and adverse event frequency

	Overall (N = 16)		Placebo (N = 5)		Canagliflozin (N = 11)	
Factor	**N**	**Statistics**	**n**	**Statistics**	**n**	**Statistics**
Hypoglycemic episodes (<70 mg/dL, n)	16		5		11	
1		2 (12.5)		0 (0.0)		2 (18.2)
Hyperglycemic episodes (>250 mg/dL, n)	16		5		11	
1		1 (6.3)		0 (0.0)		1 (9.1)
2		3 (18.8)		1 (20.0)		2 (18.2)
3		1 (6.3)		0 (0.0)		1 (9.1)
Dehydration (n)	16		5		11	
1		1 (6.3)		0 (0.0)		1 (9.1)
2		1 (6.3)		0 (0.0)		1 (9.1)
Thirst (n)	16		5		11	
1		6 (37.5)		2 (40.0)		4 (36.4)
2		1 (6.3)		0 (0.0)		1 (9.1)
Increased urination (n)	16		5		11	
1		6 (37.5)		2 (40.0)		4 (36.4)
2		1 (6.3)		0 (0.0)		1 (9.1)
Urinary tract infection (n)	16	2 (12.5)	5	1 (20.0)	11	1 (9.1)
Genital yeast infection (n)	16	2 (12.5)	5	0 (0.0)	11	2 (18.2)
Constipation (n)	16	1 (6.3)	5	0 (0.0)	11	1 (9.1)
Lightheadedness/dizzy (n)	16	2 (12.5)	5	0 (0.0)	11	2 (18.2)
Nausea (n)	16	1 (6.3)	5	0 (0.0)	11	1 (9.1)
Increased hunger (n)	16	1 (6.3)	5	1 (20.0)	11	0 (0.0)
Syncope (n)	16	1 (6.3)	5	1 (20.0)	11	0 (0.0)
Allergic reaction (n)	16	1 (6.3)	5	0 (0.0)	11	1 (9.1)
Medication compliance at 6-wk visit (%)*	8	94.5 (42.0, 100.0)	1	100.0 (100.0, 100.0)	7	91.0 (42.0, 100.0)
Medication compliance at 3-mo visit (%)*	10	90.0 (46.0, 100.0)	3	97.0 (54.0, 100.0)	7	90.0 (46.0, 98.0)
Medication compliance at 6-mo visit (%)*	8	85.5 (62.0, 100.0)	2	93.0 (86.0, 100.0)	6	85.0(62.0, 100.0)

Note. Statistics presented as median (min, max)* or N (column %).

500 kcal/d deficit.[22] The lone prospective study that investigated the effects of 3.0 mg of liraglutide reported that weight was reduced by 5.6% and 3.3% in RYGB and sleeve gastrectomy participants, respectively.[10]

As a result of the decrease in weight, body composition improved; specifically, android and truncal fat percentage were reduced by an average of 3% and 2.67%, respectively (Table 2). The reductions in android adiposity are clinically relevant because of its association with insulin resistance and cardiovascular disease risk.

The present study observed significant reductions in blood glucose (−32.90 mg/dL) after 6 months. In a similar population, another randomized controlled study observed modest reductions in blood glucose (−12 mg/dL) by comparison; in that study, patients were randomized to receive placebo or sitagliptin (100 mg) for 4 weeks.[11] If study duration was longer in the trial that investigated sitagliptin, the reductions in blood glucose may have been more marked.

Hypoglycaemic incidence is generally low with a monotherapeutic regimen of canagliflozin[23]; principally, canagliflozin improves glycaemic control by facilitating glucose excretion to a level that overlies the initial hypoglycaemic threshold (70 mg/dL).[23] There were two hypoglycaemic incidents in the present study (Table 5). Likewise, the incidence of hyperglycaemia (>250 mg/dL) was low (Table 5). However, hypoglycaemic and hyperglycaemic incidents may have been missed because of the fact that participants were not given a continuous glucose monitoring system.

Irrespective of medication class, patients diagnosed with T2D are susceptible to fractures because of defects in bone microarchitecture.[24,25] After bariatric surgery, patients may be at an increased risk for fracture occurrence because of reductions in BMD.[26] Thus, prescribing a pharmaceutical agent that does not exacerbate that risk is pertinent. Initially, a long-term study demonstrated that canagliflozin induced reductions in BMD in participants who had a BMI $\geq$ 30, multiple cardiovascular risk factors, and a T2D diagnosis.[12] However, although canagliflozin may affect BMD indirectly via the commensurate decrease in weight,[27] the literature in aggregate suggests that canagliflozin does not lead to significant reductions in

BMD.[28] Moreover, in relation to glucagon-like peptide-1 agonists, fracture risk was not accentuated in participants taking canagliflozin.[29] Although not powered to detect group differences, there were miniscule (nonsignificant) reductions in BMD in the present study; specifically, changes in BMD were negligible (Table 2). However, the drawback of the present study was that the participants were followed for 6 months. Subsequently, reductions in BMD may not have been apparent after 6 months. Furthermore, it is unclear if menopausal status impacted the results, as there were three female subjects in each group (38%) who were below the age of 50.

6 | LIMITATIONS

Given that there were no direct comparisons between canagliflozin and that of other antidiabetic medications, the study cannot indicate that canagliflozin is superior. Another limitation of the study was the inability to meet prespecified enrolment goals; furthermore, the dropouts reduced statistical power. A small sample size may preclude the ability to extrapolate the findings to the general population. Furthermore, the method used to determine adherence is not devoid of imprecision. If the subject did not return any medication, their adherence could not be quantified. Therefore, while compliance was greater than 80% (Table 5), it did not account for participants who did not return any medication. In addition, the DEXA is known to be prone to error in participants who are obese and/or after weight loss.[30] The frequency of hypoglycaemic episodes and that of other adverse events was contingent upon the participants reporting them. Not all participants were diligent with their glucometer readings. A continuous glucose monitoring device would have allowed the researchers to more readily verify hypoglycaemic and hyperglycaemic events. There was no ketone-related data to report. Finally, insulin administration represented a limitation.

7 | CONCLUSION

Weight loss, body composition, and glycaemic outcomes were improved with canagliflozin treatment. Despite a low sample size, the frequency of adverse events was low, and all were nonsevere. Even though study duration was only 6 months, decrements in BMD were minimal with short-term canagliflozin therapy. Future studies will require larger sample sizes to assess the efficacy of canagliflozin in relation to other T2D medications.

AUTHOR CONTRIBUTIONS

All authors participated in the writing of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest related to the study.

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