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Research Paper

Exploring glycosuria as a mechanism for weight and fat mass reduction. A pilot study with remogliflozin etabonate and sergliflozin etabonate in healthy obese subjects

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ABSTRACT

Inhibitors of sodium-dependent glucose co-transporter 2 (SGLT2) increase glucose excretion in the urine and improve blood glucose in Type 2 diabetes mellitus. Glycosuria provides an energy and osmotic drain that could alter body composition. We therefore conducted a pilot study comparing the effects on body composition of two SGLT2 inhibitors, remogliflozin etabonate (RE) 250 mg TID ($n = 9$) and sergliflozin etabonate (SE) (1000 mg TID) ($n = 9$), with placebo ($n = 12$) in obese non-diabetic subjects. Both drugs were well tolerated during 8 weeks of dosing, and the most common adverse event was headache. No urinary tract infections were observed, but there was one case of vaginal candidiasis in the RE group. As expected, RE and SE increased urine glucose excretion, with no change in the placebo group. All the subjects lost weight over 8 weeks, irrespective of treatment assignment. There was a reduction in TBW measured by D_2O dilution in the RE group that was significantly greater than placebo (1.4 kg, $p = 0.029$). This was corroborated by calculation of fat-free mass using a quantitative magnetic resonance technique. All but one subject had a measurable decrease in fat mass. There was significant between-subject variability of weight and fat loss, and no statistically significant differences were observed between groups. Despite a lack of a difference in weight and fat mass loss, the leptin/adiponectin ratio, a measure of insulin resistance, was significantly decreased in the RE group when compared to placebo and SE, suggesting that this SGTL-2 inhibitor may improve metabolic health independent of a change in fat mass.

Introduction

The incidence and prevalence of Type 2 diabetes (T2DM) are increasing as the result of a worldwide epidemic of obesity [1]. Medical management of patients with T2DM includes diet, exercise and weight reduction, together with oral anti-diabetic medications or insulin therapy, when appropriate [2]. Frequently, the treatment of T2DM now requires multiple agents acting via complementary mechanisms in an attempt to achieve tighter glycemic targets. Consequently, new agents with unique mechanisms of action and limited side effect profiles are needed when these targets cannot be reached [3].

Inhibitors of sodium-dependent glucose co-transporter 2 (SGLT2) reduce circulating glucose concentrations via a renal mechanism distinct from other current anti-diabetic agents [4]. SGLT2 is primarily expressed on the luminal side of the renal proximal tubule. It has high solute translocation capacity and low substrate affinity, and serves as the primary, but not exclusive, pathway for renal glucose reabsorption. Sergliflozin etabonate (SE) and remogliflozin etabonate (RE) are orally-active prodrugs of sergliflozin and remogliflozin, respectively. Sergliflozin is an SGLT2 inhibitor that increases urinary glucose excretion in a dose-dependent manner in rodents and dogs, and lowers plasma glucose levels following oral glucose challenge in diabetic rats [5]. Remogliflozin works similarly in mice and rats and exhibits antidiabetic efficacy in animal models and humans [6–8]. These two SGTL2 inhibitors have different effects on glucose excretion in humans. The maximal glycosuria observed with RE is greater than the maximal glycosuria achieved with SE [7,8].

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SGLT2 inhibitors improve plasma glucose concentrations and lower body weight in subjects with T2DM [8]. Administration of RE for 12 weeks to T2DM subjects resulted in a reduction of HbA1c of up to 1.07% versus placebo treatment, and a reduction in body weight of up to 3.51 kg (unpublished data). In another 12-week study conducted with T2DM subjects, dapagliflozin, a different SGLT2 inhibitor, improved HbA1c and produced weight changes of −2.5 to −3.4 kg compared to −1.2 kg for placebo [9]. No detailed body composition analyses were included in these studies to investigate the mechanism of the weight loss.

The renal glycosuria produced by SGLT2 inhibitors could alter body composition through loss of calories in the urine and by osmotic diuresis. In addition, initial weight changes during negative energy balance could be the result of diuresis caused by glycogen mobilization from the liver. If the sustained weight changes are the result of reduced adipose tissue stores caused by energy excretion as glucose, then this may explain, in part, the metabolic improvement seen with SGLT2 inhibitors.

The primary objective of this pilot study was to investigate the effect of RE and SE, administered for 8 weeks, on glucose excretion and body composition changes measured by quantitative magnetic resonance (QMR) [10], and by the 4-compartment (4C) body composition model [11]. In addition, we measured the changes in total body water (TBW) to determine the contribution of fluid loss caused by osmotic diuresis to the overall change in weight seen with these SGLT2 inhibitors.

Materials and methods

The study was conducted at the Addenbrookes Centre for Clinical Investigation (ACCI), Addenbrooke's Hospital, Cambridge, UK, in the GlaxoSmithKline Clinical Unit in Cambridge (CUC) and the Wellcome Trust Clinical Research Facility (WTCRF). The study was performed in accordance with Good Clinical Practice guidelines and the 1996 version of the Declaration of Helsinki and it was conducted between September 2006 and July 2007. The experimental protocols were approved by the protocol review panel at GlaxoSmithKline, the Cambridge Local Research Ethics Committee (06/Q0108/254) (EUDRACT 2006-003864-71), the Addenbrooke's Hospital R&D office, and by the WTCRF Scientific Advisory Board. All patients provided written informed consent prior to participation.

Thirty healthy subjects were recruited by direct advertisement. The sample size of this pilot study was based on feasibility. Enrollment criteria included body mass index (BMI) between 30 and 40 kg/m^2 and age between 18 and 55 years. Subjects with T2DM were excluded. The use of recreational drugs, alcohol, caffeine and strenuous exercise was forbidden. A qualified dietician advised subjects on a hypocaloric diet targeting a daily energy deficit of 2090 kJ [12] relative to the estimated daily caloric requirement of each subject, assuming a physical activity level of 1.3. After a 2 week run-in on diet alone, baseline 24 h urine glucose excretion, weight and fat mass were measured using QMR and 4C methods. Subjects were then assigned at random in a 3:3:2:2 ratio to SE 1000 mg three times daily [TID] ($n = 9$), RE 250 mg TID ($n = 9$), SE-placebo TID ($n = 6$), or RE-placebo TID ($n = 6$). Subjects were managed as outpatients and returned to the clinical unit every two weeks for eight weeks to receive counseling and to review safety endpoints. After eight weeks of dosing, they again underwent measurement of 24 h urine glucose excretion, weight and fat mass. Intermediate measurements of some pharmacodynamic endpoints were made at weeks 2, 4 and/or 6 and at a follow-up visit at week 12. Plasma sampling occurred at Week 6 to determine steady-state pharmacokinetics (PK) of RE, remogliflozin and GSK279782 (the main remogliflozin metabolite), and SE.

Fasting blood samples were collected at the beginning of the study and at clinic visits for leptin, adiponectin, IGF-1, VCAM-1.

Body composition measurements

Quantitative magnetic resonance

The characteristics of the QMR (Echo MRI-AH, Echo Medical Systems, Houston, TX, USA) have been described previously [10,13]. This methodology provides a rapid, non-invasive and highly precise measurement of human body fat using the nuclear magnetic resonance properties of protons to separate signals originating from fat and non-fat tissues. All QMR measurements were made in triplicate.

4-compartment model

Fat mass was also estimated using the following 4C equation [14]:

$$\text{Fat mass} = [2.747 \times \text{BV}] - [0.71 \times \text{TBW}] + [1.46 \times \text{BMC}] - [2.05 \times \text{BM}]$$

Where BV is body volume in liters and all other variables are in kilograms (TBW = total body water, BMC = bone mineral content, BM = body mass). BV was derived from a BOD POD™ (Life Measurement Inc, Concord, CA, USA) using estimates of % body fat and BM as follows [4]:

$$\text{BV} = (\%\,\text{fat} + 450) \times \text{BM}/495.$$

TBW was measured by D_2O dilution using a protocol designed in collaboration with the MRC Human Nutrition Research Group, Cambridge, UK, where the deuterium analysis was performed [15]. Subjects were fasted from 22:00 and at 06:00 the next morning they were awakened and asked to provide samples of saliva and voided urine for D_2O analysis. D_2O-enriched water (100 g of 7% by mass D_2O in H_2O) was then consumed, and further saliva samples were taken at 4, 5 and 6 h post dose. Up to the 6 h sample, the volume of all urine passed was recorded and assayed for D_2O content to correct for label lost from the body water pool.

Total body BMC was estimated from whole-body dual-energy x-ray absorptiometry (DXA) scans (GE Lunar Prodigy, software version 8.1 GE Lunar, Madison, WI USA).

Urinary glucose excretion

Urine was collected over 24-h intervals during clinic visits scheduled at Week 0, 2, 4, and 8, and urine samples were collected over 6-hour at Week 6 for measurement of drug concentrations. Aliquots taken from these urine collections were analyzed for urine glucose (molar units) and volume (milliliters). From these 2 measures, urine glucose excretion (mmol/24 h) and energy loss (kJ and kcal) were estimated. Urine energy loss was calculated from urine glucose excretion as follows:

Urine glucose in molar units was converted to grams by multiplying by 180.2. This value was then converted into energy in joules by multiplying by 15.76 and to kilocalories by dividing by 4.186. Urine glucose excretion on between the clinic visits was estimated using linear interpolation.

Hormone and peptide assays

The NIHR Cambridge Biomedical Research Centre, Core Biochemical Assay Laboratory analyzed the leptin and adiponectin using a two-site microtiter plate-based DELFIA assay [16], as well as IGF-1 (Siemens Healthcare Diagnostics) and VCAM-1 (Human VCAM-1 assay; R&D Systems Europe, Abingdon, UK).

Table 1
Population characteristics

		All subjects ($N = 30$)
Sex	Male, *n* (%)	22 (73%)
	Female, *n* (%)	8 (27%)
Ethnicity	White/Caucasian/ European heritage, *n* (%)	29 (97%)
	Other (not specified), *n* (%)	1 (3%)
Age, years	Mean (SD) [range]	42 (13.0) [18–63]
Weight, kg	Mean (SD) [range]	101 (14.6) [76.7–138.0]
BMI, kg/m^2	Mean (SD) [range]	33 (2.4) [30.5–40.1]
Fasting plasma glucose, mMol/L	Mean (SD) [range]	5.7 (0.59) [4.8–7.3]
Fat (QMR), kg	Mean (SD)	34 (7.3)
Fat (4C), kg	Mean (SD)	39 (7.0)
Fat free mass, kg	Mean (SD)	67 (13.7)
Total body water (D_2O), kg	Mean (SD)	47 (8.6)
Leptin/adiponectin ratio	Geometric mean (%CV)	0.0047 (150%)

Measurement of RE and SE concentrations

Blood and urine samples were collected for the determination of RE (prodrug), remogliflozin (active entity), GSK279782 (the main remogliflozin metabolite), SE (prodrug), sergliflozin (active entity) in plasma. Samples were analyzed by Worldwide Bioanalysis, GlaxoSmithKline Pharmaceuticals (Research Triangle Park, NC, USA) using protein precipitation, followed by high performance liquid chromatography tandem mass spectrometric (HPLC/MS/MS) detection [8].

Statistical analysis

Subjects from the two placebo groups were pooled into a single group for the analysis and presentation of results. The primary endpoints of the trial were change from baseline in fat mass measurements measured by QMR and the 4C model, body weight and urine glucose excretion. Endpoints were analyzed by separate mixed effect, repeated measures analysis of variance models. Terms were included for treatment group, visit, treatment-by-visit interaction, the baseline measurement, the baseline measurement-by-visit interaction and sex. Subject was fitted as a random variable. On the basis of the Akaike's Information Criterion, no specific structure was imposed on the correlations between visits. Point estimates and 95% confidence intervals were constructed using the appropriate variance term for the differences between visits within groups (e.g., estimating change from baseline for sergliflozin etabonate) for each treatment and for differences between treatments (e.g., comparing the baseline-to-Week 8 changes in the sergliflozin etabonate group with placebo). A similar model was fitted to analyze change in body weight and urine glucose excretion. Urine glucose excretion data were log-transformed for analysis because there was evidence of increasing variance with increases in urine glucose excretion. A 5% significance level was used for all analyses. No adjustments for multiplicity were made. Analysis was carried out in SAS Version 9 for Windows.

Exploratory analyses were performed to investigate the relationships between fat mass, TBW and plasma leptin and adiponectin.

Results

Thirty subjects who met the eligibility criteria were randomized into the study between October 2006 and May 2007. Baseline characteristics of the randomized subjects are given in Table 1. Of these, 27 completed the study. One subject in each treatment group withdrew consent prior to week 8 because they were unable to attend all protocol-required clinic visits. No serious adverse events were reported for the randomized subjects, and the most frequently reported adverse event was mild headache (44% for RE, 33% for SE and 50% for placebo). No urinary tract infections were observed during the study. There was one case of vaginal candidiasis occurring at the end of the 8-week treatment regimen with RE. No significant changes were observed on the safety laboratory parameters.

As previously demonstrated [5,8], both RE and SE increased urinary glucose excretion (Figure 1). The within-group increases in urine glucose excretion from baseline to Week 8 for subjects in the SE and RE groups were 247 mmol/24 h (CV: 15%) and 400 mmol/24 h (CV: 15%), respectively (both $p < 0.0001$). Furthermore, the change from baseline to Week 8 urine glucose excretion was greater with RE than with SE ($p = 0.020$). As expected, no urine glucose excretion was observed in the placebo group.

Statistically significant decreases in body mass from baseline values to Week 8 were observed for RE (−7.6 kg) and SE (−6.1 kg), but these decreases were not significantly greater than the weight loss observed in the placebo group (−5.1 kg) (Table 2). For all three treatment groups, weight loss was associated with changes of anthropometric parameters, including BMI, waist circumference and hip circumference. Consistent with the results for body weight, all treatment groups exhibited a statistically significant decrease in fat mass as measured using both QMR and the 4C model. Even though there was increased urine glucose and energy excretion produced by the SGLT2 inhibitors, there were no measurable differences of fat mass and weight relative to the placebo group (Table 2 and Figure 2A and B).

The change in fat mass by QMR was similar in all three groups (−4.1 kg, −3.4 kg and −3.1 kg, for RE, SE and placebo, respectively).

The estimated mean amounts of total energy loss over 8 weeks resulting from urine glucose excretion were 55.8 MJ (equivalent to 1.4 kg of fat), 35.4 MJ (equivalent to 0.9 kg of fat) and 0.061 MJ for the RE, SE and placebo groups, respectively. These equate to average daily values of 1000 kJ/day (240 kcal/day), 630 kJ/day (150 kcal/day) and 1.1k J/day (0.3 kcal/day) energy loss via urine for the RE, SE and placebo groups, respectively.

Figure 3 displays a comparison of the estimated total urine glucose energy loss (MJ) for each subject versus their respective fat loss converted into its energy equivalent. Across the treatment groups there was a trend for subjects who had greater energy loss through glycosuria to have a greater loss of fat mass, but this relationship was not statistically significant ($p > 0.05$).

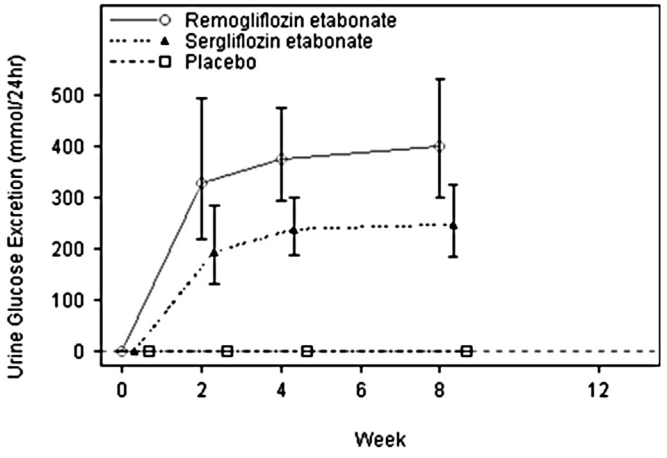

Figure 1. Urine glucose excretion over time. Urine samples were collected over 24 h at baseline, week 2, 4 and 8 study visits. Means and 95% confidence intervals are reported.

Table 2
Summary of changes from baseline to week 8

Endpoint	Placebo	Remogliflozin etabonate	Sergliflozin etabonate	Difference from placebo	
	$N = 11$	$N = 8$	$N = 8$	Remogliflozin etabonate	Sergliflozin etabonate
Weight (kg)	−5.1 (−7.1, 3.2) $p < 0.001$	−7.6 (−10.0, −5.2) $p < 0.001$	−6.1 (−8.4, −3.8) $p < 0.001$	−2.5 (−5.6, +0.6) $p = 0.105$	−1.0 (−3.9, +2.0) $p = 0.511$
Fat mass (QMR) (kg)	−3.4 (−4.9, −2.0) $p < 0.001$	−4.1 (−5.9, −2.3) $p < 0.001$	−3.1 (−4.8, −1.4) $p < 0.001$	−0.7 (−3.0, +1.7) $p = 0.565$	+0.3 (−1.9, +2.5) $p = 0.786$
Fat free mass (QMR) (kg)	−1.5 (−2.3, −0.7) p < 0.001	−2.7 (−3.7, −1.8) $p < 0.001$	−2.2 (−3.2, −1.3) $p < 0.001$	−1.3 (−2.5, −0.0) $p = 0.048$	−0.8 (−2.0, +0.5) $p = 0.209$
Fat mass (4C) (kg)	−4.6 (−6.5, −2.7) $p < 0.001$	−4.8 (−7.2, −2.5) $p < 0.001$	−3.8 (−6.1, −1.6) $p = 0.002$	−0.2 (−3.1, +2.8) $p = 0.906$	+0.8 (−2.0, +3.7) $p = 0.564$
Total body water (D_2O) (kg)	−0.3 (−1.1, +0.5) $p = 0.434$	−1.7 (−2.6, −0.8) $p = 0.001$	−1.1 (−2.0, −0.1) $p = 0.025$	−1.4 (−2.6, −0.2) $p = 0.029$	−0.8 (−2.0, +0.5) $p = 0.206$
Leptin/adiponectin ratio (%)	−7% (−37%, +36%) $p = 0.685$	−46% (−62%, −22%) $p = 0.006$	−3% (−31%, +36%) $p = 0.822$	−41% (−65%, −2%) $p = 0.033$	+4% (−37%, +72%) $p = 0.704$
BMI ($kg/m^{2)}$	−1.7 (−2.3, −1.0)	−2.4 (−3.1, −1.6)	−2.0 (−2.7, −1.3)		
Hip (cm)	−3.1 (−5.1, −1.2)	−3.0 (−7.4, +1.4)	−1.9 (−6.2, +2.5)		
Waist (cm)	−2.8 (−6.3, +0.7)	−4.2 (−9.5, +1.2)	−4.6 (−6.9, −2.2)		
Weight lost as fat, % (QMR)	63% (44%, 83%)	57% (41%, 73%)	65% (40%, 89%)		

Values are mean (except for leptin/adiponectin ratio which is geometric mean), 95% confidence interval, and *p*-values for key endpoints.
Fat free mass calculated as weight − fat mass (QMR).
Weight lost as fat calculated as 100 × fat loss (QMR).

The line in Figure 3 indicates the theoretical negative energy balance resulting from the dietary restriction (500 kcal/day; 2090 kJ/day on each of 56 days = 117 MJ) plus any given urine glucose excretion (e.g., a subject with estimated urine glucose excretion of 30 MJ has a projected total energy loss of 147 MJ). The theoretical projections can be seen to lie centrally within the spread of the observed data points.

The measurements of TBW before and after 8 weeks of dosing are reported in Table 2. Compared to baseline, there were statistically significant reductions of TBW of 1.7 kg and 1.1 kg for RE and SE, respectively, but there was no change in the placebo group. Compared to placebo, there was a statistically significant reduction of TBW with RE, but not SE.

No treatment-related changes in mean adiponectin and IGF-1 concentrations were observed. Baseline leptin concentrations were related to baseline fat mass measurements, and leptin concentrations decreased over the course of the study. The changes in leptin concentration were consistent with fat mass changes in all the treatment groups. There was a trend for mean VCAM-1 levels to increase over the course of the study for all treatment regimens (data not shown).

The leptin/adiponectin ratio (LAR) decreased by 46% from baseline to Week 8 in the RE group, and this was significantly more than was seen in the placebo (−7%) or SE (−3%) groups (Table 2).

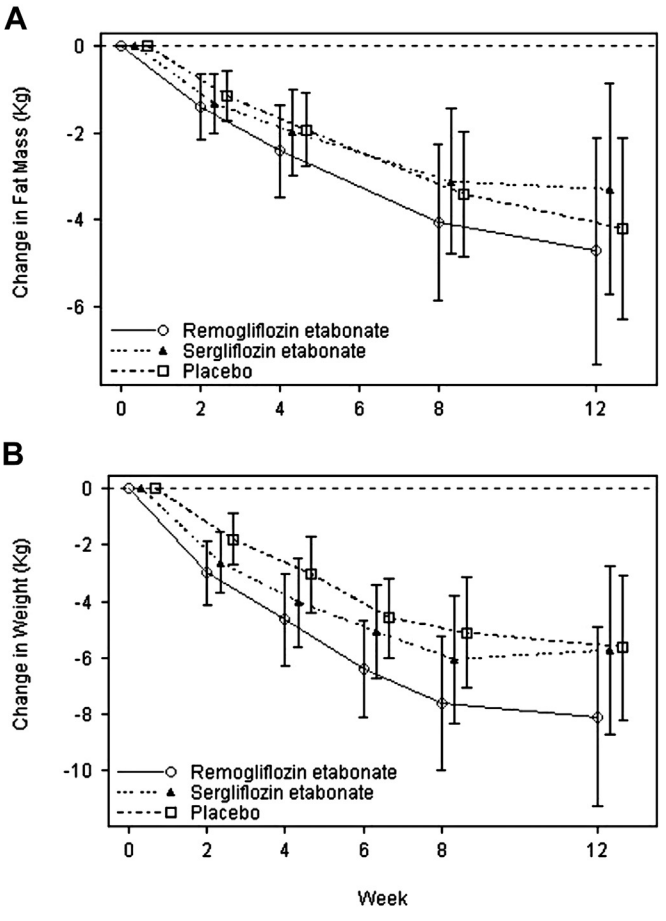

Figure 2. (A) Changes in fat mass over time Fat mass was measured in triplicate by QMR at baseline, week 2, week 4 and week 8 study visits. Means and 95% confidence intervals are shown. (B) Changes in weight over time body weight was measured at baseline, week 2, week 4 and week 8 study visits. Means and 95% confidence intervals are shown.

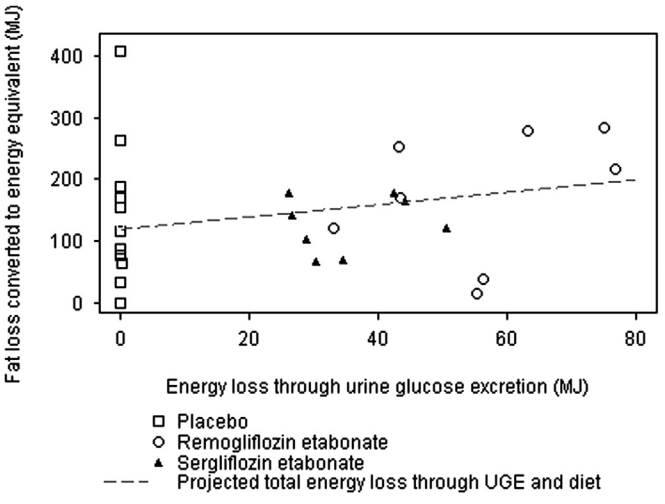

Figure 3. Relationship between urine glucose excretion and loss of fat mass over 8 weeks. Individual subject values of glycosuria and QMR fat mass changes have been converted to energy equivalents (MJ).

This difference was primarily driven by decreases in leptin (Figure 4).

Pharmacokinetic analyses at Week 6 confirmed that the steady-state exposures of RE and SE in this obese population (data not shown) were comparable to those previously reported in diabetic patients and normal lean volunteers [8].

Discussion

At the time this study was designed there was not information on the effects of SGLT2 inhibitors in obese humans. As a result, we investigated the actions of two SGTL2 inhibitors with different effects on glucose excretion in obese, non-diabetic subjects, and attempted to relate the energy lost through glycosuria to changes in weight and body composition as assessed by the state-of-the-art methods, QMR and the 4C model. Previously, we had demonstrated that QMR was the most precise way of detecting changes fat mass [10,13]. We also used D_2O dilution to measure TBW to quantify the fluid shifts produced by SGLT2 inhibition in these non-diabetic subjects. After we started our study, two SGLT2 inhibitors have been shown to cause weight loss in T2DM subjects. Administration of RE for 12 weeks to T2DM subjects resulted in reductions in body weight of up to 3.5 kg compared to placebo, in addition to lowering HbA1c, but no data were collected on body composition changes (unpublished data). Dapagliflozin administered for 24 weeks to T2DM patients reduced total body weight and fat mass [9].

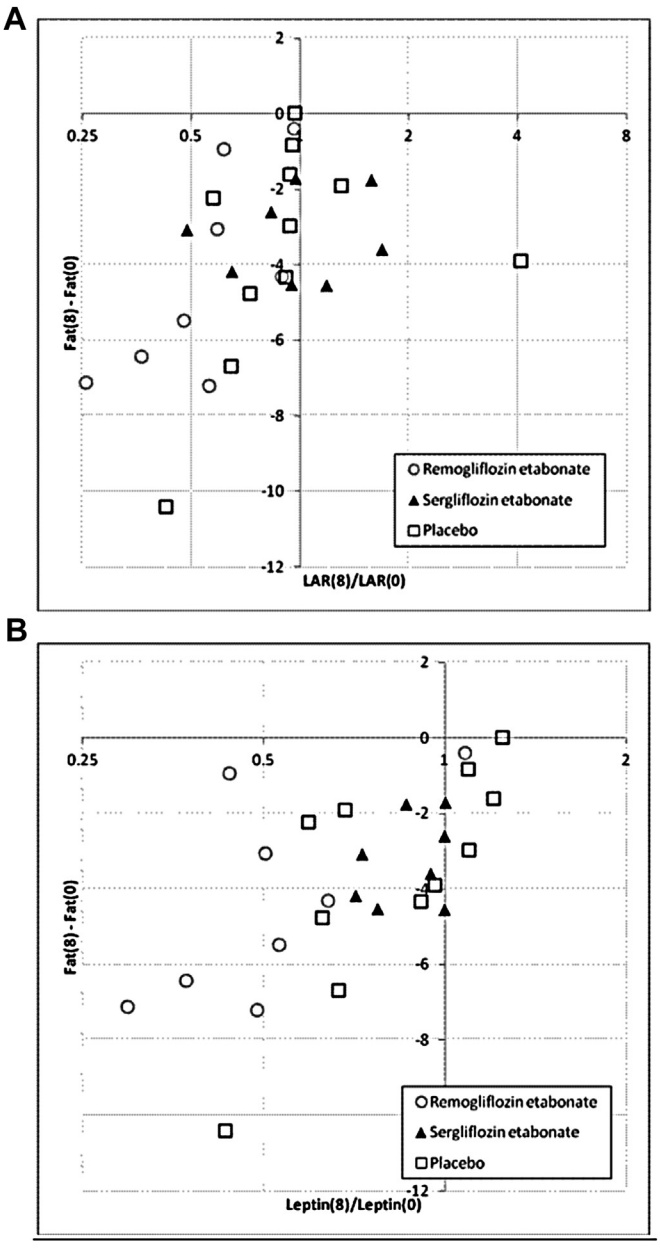

Figure 4. Correlation of leptin/adiponectin, leptin and fat mass. Correlation of change of leptin /adiponectin ratio (LAR) versus change of fat mass (week 8–week 0) (A) and of change of leptin versus change of fat mass (week 8–week 0) (B).

In the present study, we have extended the initial observations of the actions of SGLT2 inhibitors to obese non-diabetic subjects. As anticipated, there was a statistically significant treatment-related effect of RE and SE on urine glucose excretion, with RE producing greater urine glucose excretion than SE, as expected from the differences in drug exposure and potency of the two inhibitors. There was no change in glucose excretion in the placebo groups. These treatment- and visit-related changes in urine glucose excretion translate to mean differences in urine energy loss of 55.8 MJ, 35.4 MJ and 0.06 MJ for the RE, SE and placebo groups, respectively. In contrast, urine volume measures were relatively consistent among treatment groups and stable over the treatment periods (data not shown).

All the obese subjects lost weight over 8 weeks, irrespective of treatment assignment, and all but one subject had a measurable decrease in fat mass. Notably, the degree of weight and fat loss varied considerably between individuals (e.g., weight loss on placebo ranged from 1.3 to 11.9 kg over the eight weeks period). In light of this large between-subject variation and the small size of the study population, it is not surprising that there were no statistically significant differences between active treatment and placebo groups with regard to weight or fat loss. The weight changes in these subjects would be expected to result from the difference between energy intake and energy expenditure or energy loss as glycosuria. In our study, the protocol required a behavioral modification that should have resulted in a negative daily energy intake of 2090 kJ (500 calories) for all subjects over the duration of the trial. In addition, the estimated mean total daily energy loss as glycosuria was approximately 1000 kJ/day (240 kcal/day), 630 kJ/day (150 kcal/day) and 1.1 kJ/day (0.3 kcal/day) for the RE, SE and placebo groups, respectively. Furthermore, the RE group at week 8 showed a reduction in TBW measured by D_2O that was significantly greater than placebo (1.4 kg, $p = 0.029$). This was corroborated by calculation of fat-free mass (weight − fat mass measured by QMR) which remained unchanged in the placebo group at 8 weeks, but was significantly decreased in the SGTL-2 inhibitor-treated groups. We found that the changes in fat-free mass correlated with TBW changes ($r = 0.55$), but the former seemed to decrease more in the SGLT2 treated groups than TBW changes. We have no data on changes on glycogen storage, but these would occur early and would be expected to have little impact on absolute hydration status at the end of 8 weeks of treatment.

The size of the study population was limited, but taken together these data suggest two possibilities for the lack of differentiation of the weight changes seen with the SGLT2-treated and placebo-treated subjects: (i) placebo-treated subjects were more compliant with the behavioral modifications required by the protocol, creating a more variable, and in some cases greater, negative energy balance, and/or (ii) the SGLT2 inhibitors stimulated food intake as a compensation for the energy loss as glycosuria, and this was large enough to overshadow the weight loss from urinary calorie loss and osmotic diuresis. The food intake and energy expenditure information collected during the study by the dieticians was not sufficiently detailed to investigate this possibility. However, it has been reported that SGLT2 inhibition may increase food intake in an animal model of obesity [17].

The leptin/adiponectin ratio has been proposed as a measure of insulin resistance in non-diabetic individuals [18], and it was surprising that there was a significant decrease between baseline at the end of the intervention in the RE group when compared to placebo and SE, suggesting that this SGTL-2 inhibitor improved metabolic health independent of a significant change in fat mass. The difference between the RE and SE groups may indicate that the degree of glycosuria may be important in activating a novel mechanism leading to the reduction of the leptin-adiponectin ratio.

In conclusion, we have demonstrated that administration of SGLT2 inhibitors to obese non-diabetic subjects increases energy loss via urine glucose excretion. We observed statistically significant and comparable reductions of weight and fat mass in the SGLT2 and placebo groups which may indicate that SGLT2 inhibition drives some compensatory increase in energy intake. In addition, RE produced a statistically significant reduction of fat-free mass and TBW. The reduction of the leptin-adiponectin ratio suggests that RE, but not SE, treatment is capable of improving the metabolic status of on non-diabetic obese subjects. As this was a small pilot study, a long-term weight loss trial would be required to confirm our observations. Ideally, the trial would thoroughly assess energy balance and monitor food intake and energy expenditure, to allow deconvolution of the factors contributing to the variability between individuals in response to an SGLT2 inhibitor. The favorable body composition and metabolic changes in non-diabetic obese subject should be investigated further when SGLT2 inhibitors are used as monotherapy or when combined with other weight loss treatments.

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