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No evidence of compensatory changes in energy balance, despite reductions in body weight and liver fat, during dapagliflozin treatment in type 2 diabetes mellitus: A randomized, double-blind, placebo-controlled, cross-over trial (ENERGIZE)

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Abstract

Aim: This study assessed the impact of dapagliflozin on food intake, eating behaviour, energy expenditure, magnetic resonance imaging (MRI)-determined brain response to food cues and body composition in patients with type 2 diabetes mellitus (T2D).

Materials and Methods: Patients were given dapagliflozin 10 mg once daily in a randomized, double-blind, placebo-controlled trial with short-term (1 week) and long-term (12 weeks) cross-over periods. The primary outcome was the difference in test meal food intake between long-term dapagliflozin and placebo treatment. Secondary outcomes included short-term differences in test meal food intake, short- and long-term differences in appetite and eating rate, energy expenditure and functional MRI brain activity in relation to food images. We determined differences in glycated

Surya Panicker Rajeev, Carl Alexander Roberts these 2 authors contributed equally to the manuscript and are sharing lead authorship.

haemoglobin, weight, liver fat (by ^{1}H magnetic resonance spectroscopy) and subcutaneous/visceral adipose tissue volumes (by MRI).

Results: In total, 52 patients (43% were women) were randomized; with the analysis of 49 patients: median age 58 years, weight 99.1 kg, body mass index 35 kg/m^2, glycated haemoglobin 49 mmol/mol. Dapagliflozin reduced glycated haemoglobin by 9.7 mmol/mol [95% confidence interval (CI) 3.91-16.27, $p = .004$], and body weight (−2.84 vs. −0.87 kg) versus placebo. There was no short- or long-term difference in test meal food intake between dapagliflozin and placebo [mean difference 5.7 g (95% CI −127.9 to 139.3, $p = .933$); 15.8 g (95% CI −147.7 to 116.1, $p = .813$), respectively] nor in the rate of eating, energy expenditure, appetite, or brain responses to food cues. Liver fat (median reduction −4.7 vs. 1.95%), but not subcutaneous/visceral adipose tissue, decreased significantly with 12 weeks of dapagliflozin.

Conclusions: The reduction in body weight and liver fat with dapagliflozin was not associated with compensatory adaptations in food intake or energy expenditure.

KEYWORDS
dapagliflozin, clinical trial, appetite control, SGLT2 inhibitor, energy regulation

1 | INTRODUCTION

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) have become an established pharmacological treatment for type 2 diabetes (T2D)[1–4] with glucose- and weight-lowering effects,[2,3,5–7] conferring cardiovascular and reno-protective benefits.[8–15] As such their use has been extended to other clinical populations, such as those with chronic kidney disease and/or heart failure, with/without T2D.

SGLT2 inhibition results in a typical daily net urinary glucose excretion of ∼75 g with a daily energy loss of ∼300 kcal (1200 kJ/day).[16,17] Thus, the predicted weight loss after 24 weeks of treatment with the SGLT2i dapagliflozin (assuming no compensatory changes in food intake, energy expenditure and no diuresis), based on the calculated energy loss, would be ∼7 kg. However, clinical data so far suggest that the observed total weight loss with dapagliflozin 10 mg dose is substantially less (∼2.5-3.2 kg[18–20]). These data suggest that there are compensatory mechanisms that attenuate weight loss with chronic treatment,[21] e.g. an increase in food intake and/or a reduction in energy expenditure. Preclinical studies provide evidence for compensatory mechanisms, for example, in SGLT2 knockout mice energy expenditure is higher and respiratory quotient lower, consistent with a shift from carbohydrate to fat metabolism with compensatory increases in feeding and drinking.[22] Human studies also showed a shift from carbohydrate to fat metabolism.[23]

Studies examining the effect of SGLT2i on appetite and energy expenditure in humans are sparse. In the recent randomized, double blind, placebo-controlled SEESAW study, the effects of empagliflozin 25 mg once daily for 24 weeks were compared with those of placebo, placebo plus dietary restriction (to match the energy deficit elicited by SGLT2i), and with a combination of empagliflozin and dietary restriction. Despite significant changes in weight (placebo, 0.44 kg; placebo plus diet, 1.91 kg; empagliflozin, 2.22 kg; and empagliflozin plus diet, 5.74 kg), there were no between-group differences in the primary outcome measure, change in postprandial circulating total peptide-YY (PYY) during a 3-h mixed-meal tolerance test, from baseline to 24 weeks. Similarly, there were no differences in postprandial total glucagon-like peptide-1 (GLP-1), acylated ghrelin, subjective appetite perceptions or other key components of energy balance.[24] It is important to understand these physiological mechanisms that underpin this attenuation of weight loss with SGLT2i therapy to maximize the weight loss achievable with this class of drugs in people with T2D, but the results of this study point against a role of changes in postprandial appetite-regulatory gut peptides.

The ENERGIZE trial was designed to test directly the hypothesis that 12 weeks of treatment with the SGLT2i, dapagliflozin 10 mg daily, in individuals with T2D would cause a compensatory increase in food intake, compared with placebo, that would attenuate the anticipated weight loss. Short-term (1 week) and long-term (12 weeks) changes in food intake and appetite (within meal and across the day) using test meals and visual analogue scales (VAS) were assessed. Energy expenditure using indirect calorimetry, brain reactivity to images of hedonic foods with functional MRI (fMRI) and abdominal MRI-determined changes in body composition [subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) volumes and liver fat] to assess adaptive responses to glycosuria-induced negative energy balance were also assessed as secondary outcome measures.

2 | MATERIALS AND METHODS

2.1 | Trial design and study participants

This was an outpatient, double-blind, placebo-controlled cross-over study. Fifty-two participants with T2D were recruited: aged

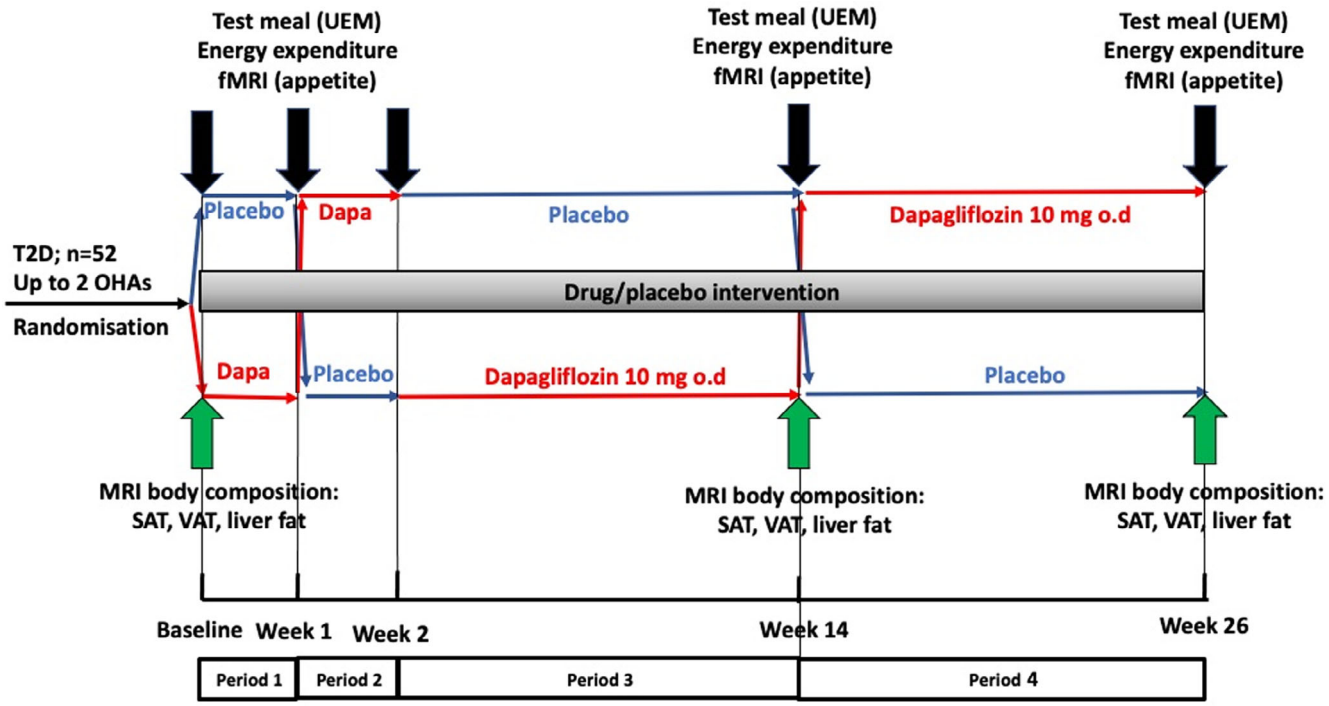

FIGURE 1 Study protocol schematic. fMRI, functional magnetic resonance imaging; OHA, Oral hypoglycemic agents; SAT, subcutaneous adipose tissue; T2D, type 2 diabetes mellitus; UEM, Universal Eating Montor; VAT, visceral adipose tissue.

18-75 years, with glycated haemoglobin (HbA1c) ≥ 6.5% (48 mmol/mol) or ≥7.0% (53 mmol/mol) in patients treated without or with sulphonylureas, respectively, but <11% (97 mmol/mol). After routine screening tests, each participant visited the study centre on 12 occasions. All participants received 7 days of either dapagliflozin or placebo for short-term assessments, followed by 12 weeks of each treatment for long-term assessments. Each participant served as their own control with the cross-over between drug and placebo at the short-term and long-term assessment points. The 7-day cross-over measurements were designed to assess short-term effects of treatment on compensatory mechanisms (at a time point where significant weight loss would not have yet occurred), while the long-term cross-over was designed to investigate compensatory mechanisms during the dynamic weight loss phase (Figure 1).

The full trial protocol has already been published.[25]

2.2 | Study design

As shown in the schematic (Figure 1), the study consisted of four time periods. All participants received dapagliflozin and placebo for the short- and long-term studies, over 7-10 days, with a cross-over period of 12 weeks. Forty-five participants completed the study protocol, 49 were analysed as per the pre-specified modified intention-to-treat analysis that included all participants who took at least one dose of study drug (Figure 2).

2.2.1 | Biochemistry and haematology

Blood samples were taken for liver function, lipid profile, thyroid function, HbA1c and haematology (full blood count), at baseline to ensure screening criteria were met, and at the end of each long-term treatment period.

2.2.2 | Test meals and appetite assessments

On each of the test meal and appetite assessment days, participants attended the lab at 8 a.m. and confirmed that they had had nothing to eat or drink other than water from midnight the previous evening. At 9 a.m. participants were served a fixed load breakfast as per Halford et al.[26] (for full nutrition information and standard operating procedure see Supporting Information). Participants were asked to rate their degrees of hunger, fullness, satisfaction, desire to eat, perception of how much they could eat (prospective consumption) and nausea on a 100-mm VAS scale pre- and post-breakfast and at 10 a.m., 11 a.m., 12 noon, 3 p.m., 4 p.m. and 5 p.m.

At 1 p.m. participants were given a test meal consisting of pasta with a tomato-based sauce (for full nutritional information and standard operating procedure see Supporting Information). Participants were told to eat ad-libitum until they were comfortably full and to signal to the experimenter when they had finished. Food intake and within-meal assessment of appetite (hunger, fullness,

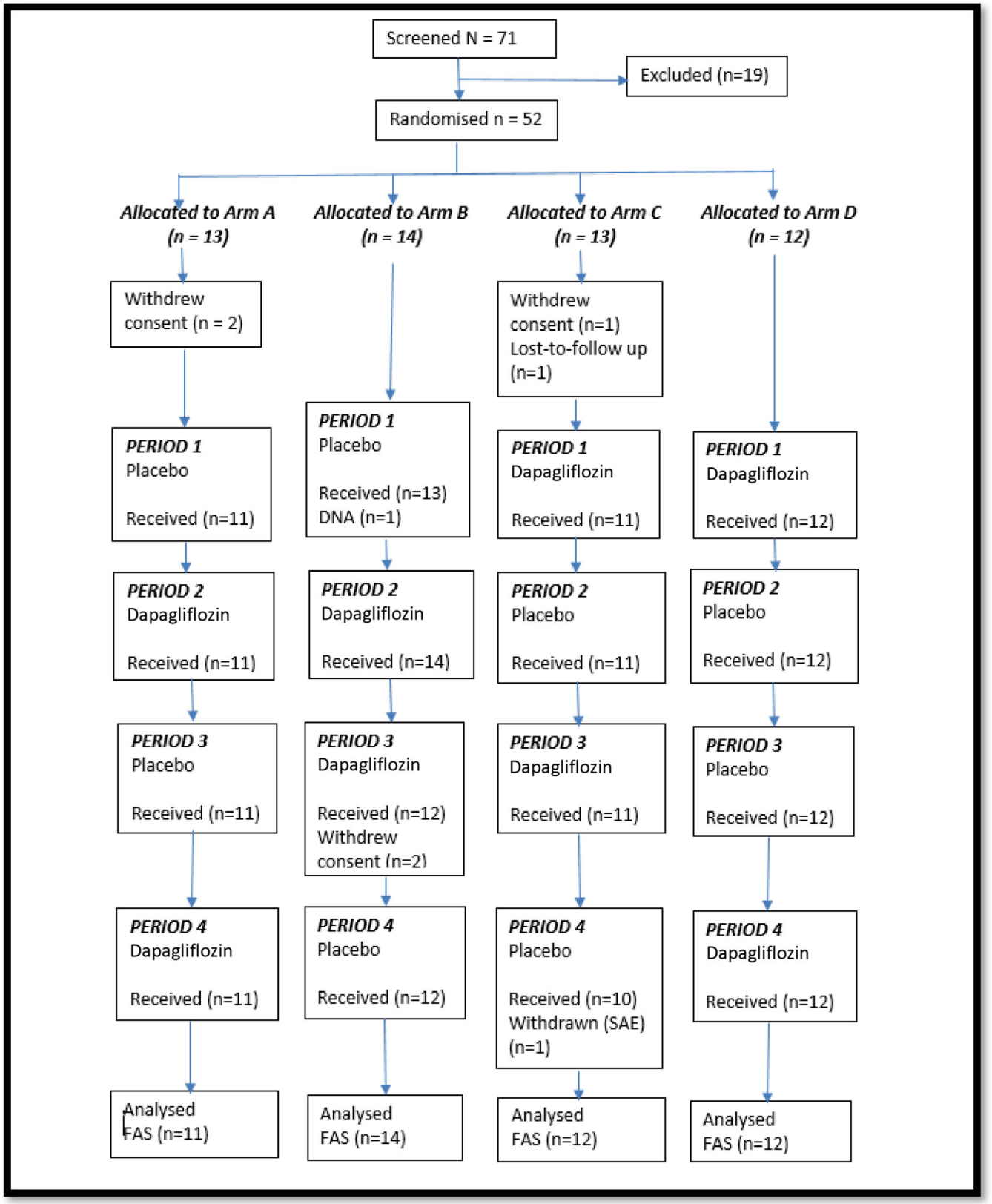

FIGURE 2 CONSORT diagram explaining patient flow through the study. FAS, Full Analysis Set.

desire to eat and prospective consumption) were collected using VAS and the Sussex Ingestion Pattern Monitor (SIPM V.2.0.13; University of Sussex). Rate of eating was calculated in grams per second, and satiety quotient was calculated by dividing the difference of pre- and post-meal hunger by the total weight of food consumed.

2.2.3 | Indirect calorimetry

Energy expenditure and respiratory exchange ratio (RER) were assessed by indirect calorimetry using a ventilated hood system (GEM Nutrition Limited). Measurements were started after the participant had been under the hood for 5 min to allow for acclimatization, and data were collected over a 20-min period. Indirect calorimetry was performed pre- and post-breakfast and at 10 a.m., 11 a.m., 12 noon, 3 p.m., 4 p.m. and 5 p.m.

2.2.4 | Magnetic resonance methods

After screening for MRI contraindications, participants underwent MR scanning at the Liverpool Magnetic Resonance and Imaging Centre (LIMRIC), part of Liverpool Shared Research Facilities, in the University of Liverpool Faculty of Health and Life Sciences. Brain fMRI used a 3.0 T Trio scanner (Siemens Healthineers), and body composition and liver fat measurements used a 1.5 T Symphony scanner (Siemens Healthineers).

2.2.5 | Functional magnetic resonance imaging

fMRI data were acquired at 7 days and 12 weeks of dapagliflozin/placebo treatment. Participants fasted from 10 p.m. the previous night and undertook a fasted scan at 9 a.m. in which blood oxygen level-dependent responses were recorded to view passively the sets of images of high-calorie (hedonic) foods versus non-food control objects (high calorie foods > control – first level contrast) in the fasted state, then again 1 h after consuming a fixed load breakfast. The results were analysed using the following comparisons (second-level analysis): (a) dapagliflozin > placebo, at scan 1 (pre-breakfast/fasted) after 7 days treatment; (b) dapagliflozin > placebo at scan 2 (post-breakfast) after 7 days treatment; (c) dapagliflozin > placebo at scan 1 (pre-breakfast) after 12 weeks treatment; and (d) dapagliflozin > placebo at scan 2 (post-breakfast) after 12 weeks treatment.

In each case the significance level was set at $p < .05$, whole-brain corrected for family-wise error rate. The minimum cluster size threshold was not specified. Analysis was limited to 17 participants who completed all necessary scans for analysis of short-term treatment (dapagliflozin vs. placebo at 1 week), and 17 participants who completed all necessary scans for analysis of long-term treatment (dapagliflozin vs. placebo at 12 weeks). For further details of fMRI methods and analysis see Supporting Information.

2.2.6 | Assessment of body composition

Body composition and liver fat was assessed at baseline, and at 14 and 26 weeks. Liver fat (intrahepatocellular triglyceride) was measured by ^{1}H magnetic resonance spectroscopy. Body fat volume, compromising abdominal SAT and abdominal VAT, were measured by MRI. For details of MRI and ^{1}H magnetic resonance spectroscopy methods see Supporting Information.

2.3 | Statistical analysis

2.3.1 | Sample size calculation

The primary outcome measure was energy intake after 12 weeks. Based on previous research[26] and using PROC POWER in SAS V.9.3, we estimated that 52 participants were required to detect a 12.5% change in food intake by paired t-test with 80% power at a two-sided 5% level of significance (based on a correlation between measurements of 0.7 and a between-participant SD of 165 g). The 12.5% change in food intake assumes a baseline test meal consumption of 460 g, with a 12.5% change equating to a 57.5 g increase in food intake. This calculation allows for 20% participant dropout.

2.3.2 | Body composition

For changes in body composition, only the differences in MRI determined abdominal SAT and abdominal VAT and liver fat were measured between visit 4 (14 weeks) and visit 5 (26 weeks). Results of the two groups who received 12 weeks of placebo (groups B/C) and 12 weeks of dapagliflozin (groups A/D) were pooled. Comparison with the baseline scan visit 1 was not deemed appropriate as all four treatment groups had received 1 week of dapagliflozin in the acute study period.

3 | RESULTS

3.1 | Screening and randomization

Of 71 participants screened from August 2015 to August 2017, 52 were randomized to the study. The 49 participants who took at least one dose of study medication were included in the final analysis.

3.2 | Demographic characteristics

The mean age of participants was 57.3 years (SD 9.4) and 63% were men. All but one participant were of white ethnicity (Table 1).

3.3 | Details of diabetes treatment

Of 49 participants (four were on diet only, 44 were on metformin, 15 were on sulphonylurea: gliclazide and four were on dipeptidyl peptidase-4 inhibitors: three sitagliptin, one linagliptin); 14 were on a

TABLE 1 Demographic characteristics, haematology/biochemistry and body composition of the study participants

Demographic characteristics		
Age, mean (SD)		57.3 (9.4)
Gender, n (%)		
Female		18 (37)
Male		31 (63)
Ethnicity, n (%)		
White		48 (98)
African		1 (2)
Smoking status, n (%)		
Current smoker		4 (8)
Ex-smoker		20 (41)
Never smoked		25 (51)
Alcohol status, n (%)		
None		7 (14)
Regular		29 (59)
Haematology/biochemistry, n/mean (SD)		
Glycaemic parameters		
HbA1c, mmol/mol	49	60.4 (11.2)
Renal/electrolytes		
Sodium, mmol/L	46	140 (2)
Potassium, mmol/L	45	4.5 (0.4)
Urea, mmol/L	46	5 (1.2)
Creatinine, μmol/L	46	74 (14)
eGFR, ml/min/1.73 m^2	46	82 (9)
Liver		
Bilirubin, μmol/L	46	9 (4.5)
Alanine transaminase, IU/L	45	36 (20)
Alkaline phosphatase, IU/L	46	77 (19)
Albumin, g/L	46	45 (7)
Other		
Haemoglobin, g/L	46	141 (13)
Body mass and composition		
Weight, kg	49	101.7 (18.5)
Body mass index, kg/m^2	49	35.2 (5.6)
Subcutaneous adipose tissue volume, L	27	7.5 (3.3)
Visceral adipose tissue volume, L	27	5.1 (2.5)
Liver fat, %	32	19.9 (16)

Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin.

combination of metformin and gliclazide and four were on a combination of metformin and sitagliptin/linagliptin (Figure 3).

3.4 | Biochemical and anthropometric characteristics

The mean baseline weight of the study participants (n = 49) was 107 kg (SD 18.5) and body mass index was 35.2 kg/m^2 (SD 5.6).

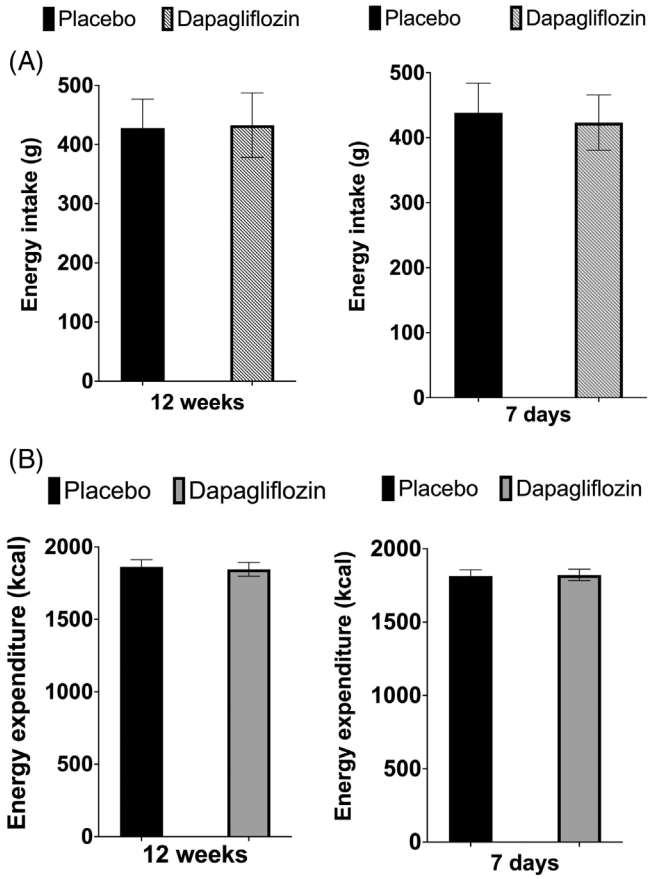

FIGURE 3 Long-term and short-term changes in (A) energy intake, and (B) energy expenditure with dapagliflozin (hatched bars) versus placebo (black bars).

The mean HbA1c was 60.4 mmol/mol (SD 11.2) and mean estimated glomerular filtration rate was 82.3 (SD 9.1).

3.5 | Primary outcome measure: food intake

3.5.1 | Effects of dapagliflozin on food intake during standard test meal after 12 weeks treatment

There was no difference in food intake between dapagliflozin and placebo treatment after 12 weeks (Figure 3). The mean food intake of participants in the test meal during dapagliflozin treatment was 433 g, compared with 428 g during placebo treatment [mean (SE) treatment difference 5.7 (67), 95% confidence interval (CI) −128 to 139, $p = .93$].

3.6 | Secondary outcome measures

3.6.1 | Clinical end points

Dapagliflozin reduced HbA1c by 9.7 mmol/mol (95% CI 3.91-16.27, $p = .004$), and body weight (−2.84 vs. −0.87 kg) versus placebo.

TABLE 2 Within-meal appetite measures at 7 days and 12 weeks.

	7 days						12 weeks					
	n	Placebo mean	n	Dapa mean	*p*	95% CI	n	Placebo mean	n	Dapa Mean	*p*	95% CI
Rate of eating, g/s	43	0.91	43	0.82	.51	(−0.31, 0.16)	41	0.91	43	0.90	.97	(−0.23, 0.24)
Satiety quotient	47	0.13	46	0.12	.98	(−2.76, 2.70)	43	0.70	43	2.14	.36	(−1.53, 4.15)

TABLE 3 Mean appetite measures (of 100 on Visual Analogue Scales) across the day at 7 days and 12 weeks

	7 days						12 weeks					
	n	Placebo mean	n	Dapa mean	*p*	95% CI	n	Placebo mean	n	Dapa mean	*p*	95% CI
Hunger	47	29.67	48	31.04	.30	(−1.54, 4.97)	45	32.18	46	30.62	.34	(−4.99, 1.73)
Fullness	47	56.22	48	55.58	.59	(−4.55 2.59)	45	56.98	46	56.54	.72	(−4.35, 3.01)
Prospective consumption	47	31.85	48	31.69	.94	(−2.95, 3.17)	45	33.34	46	32.63	.64	(−3.91, 2.40)
Desire	47	31.93	48	31.69	.90	(−3.13, 3.54)	45	34.03	46	33.46	.84	(−3.80, 3.08)
Thirst	47	32.17	48	32.42	.95	(−2.91, 2.73)	45	32.00	46	33.68	.43	(−1.76, 4.06)
Satisfaction	47	62.69	48	61.57	.46	(−4.44, 2.04)	45	61.45	46	60.23	.32	(−5.03, 1.64)
Nausea	47	5.44	48	5.36	.99	(−4.08, 4.11)	45	10.16	46	7.14	.17	(−7.20, 1.25)

3.7 | Energy balance

3.7.1 | Effects of dapagliflozin on food intake during standard test meal after 7 days treatment

There was no difference in food intake between dapagliflozin and placebo treatment after 7 days (Figure 3). The mean food intake in the test meal during dapagliflozin treatment was 423 g compared with 438 g during placebo treatment [mean (SE) treatment difference −16 (67), 95% CI 148 to 116, $p = .81$].

3.7.2 | Effect of dapagliflozin on within-meal measures of appetite at 7 days and 12 weeks

There was no difference in the rate of eating or satiety quotient between dapagliflozin and placebo treatment in the short term or long term (Table 2). There was no difference in within-meal hunger, fullness, prospective consumption or desire to eat scores between dapagliflozin and placebo at 7 days or 12 weeks.

3.7.3 | Effect of dapagliflozin on appetite fluctuation across the day at 7 days and 12 weeks

There were no differences in hunger, fullness, prospective consumption, desire, thirst, satisfaction, or nausea across the day at 7 days or 12 weeks (see Table 3 for *p*-values and CIs).

3.7.4 | Effect of dapagliflozin on energy expenditure and respiratory exchange ratio at 7 days and 12 weeks

There were no differences in total energy expenditure between dapagliflozin and placebo treatment in the short-term period of 7 days (95% CI −22.22 to −41.63, $p = .54$), or the long-term period of 12 weeks, (95% CI −49.43 to 18.43, $p = .37$) (Figure 3). After 7 days treatment, dapagliflozin had a significantly lower mean RER compared with placebo (0.92 vs. 0.97 respectively, 95% CI −0.10 to −0.02, $p = .003$). This difference was not seen at 12 weeks (95% CI −0.05 to 0.03, $p = .47$).

3.8 | Body composition

3.8.1 | Effect of dapagliflozin on body composition and liver fat at 12 weeks

Liver fat

There was a significant reduction in median liver fat between participants treated with dapagliflozin [−4.7% (−6.475, 0.25)] compared with placebo [1.95 (−0.15, 5.4)] between weeks 14 and 26; $p = .033$ (Table 4).

Subcutaneous/visceral adipose tissue

There was no significant reduction in median VAT or SAT volumes fat between participants treated with dapagliflozin compared with placebo between weeks 14 and 26 (Table 4).

TABLE 4 Changes in liver fat and VAT and SAT with dapagliflozin and placebo

	Placebo (groups B and C), median (IQR)/N	Dapagliflozin (groups A and D), median (IQR)/N	*p*
Liver fat, %			
Visit 4	5.85 (2.83, 16.75)[14]	19.45 (8.73, 34.25)[14]	
Visit 5	14.4 (3.53, 18.35)[10]	21.05 (7.3, 29.58)[12]	
Visit 5-visit 4	1.95 (−0.15, 5.4)[10]	−4.7 (−6.475, 0.25)[12]	.033
VAT			
Visit 4	4.863 (2.91, 6.38)[14]	4.235 (2.991, 7.16)[14]	
Visit 5	4.865 (2.66, 6.41)[12]	4.218 (3.224, 6.306)[11]	
Visit 5-visit 4	−0.073 (−0.36, 0.19)[12]	−0.032 (−0.307, 0.11)[11]	.611
SAT			
Visit 4	6.36 (5.41, 8.65)[14]	6.743 (5.234, 7.637)[14]	
Visit 5	5.932 (5.05, 8.31)[12]	6.224 (4.528, 7.184)[11]	
Visit 5-visit 4	−0.084 (−0.332, 0.005)[12]	−0.005 (−0.322, 0.159)[11]	.998

Abbreviations: IQR, interquartile range; N, number scanned in substudy; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

3.9 | Brain activity in response to food

3.9.1 | Effect of dapagliflozin on dapagliflozin on neurophysiological response to food cues at 7 days and 12 weeks (functional magnetic resonance imaging)

There were no significant differences in brain activation between dapagliflozin and placebo treatment in any of the four contrasts specified in Section 2 Materials and methods.

3.10 | Adverse events

There were five serious adverse events during the study period with placebo/treatment: two non-ST elevation myocardial infarction, one atrial fibrillation, one abdominal pain of unknown cause and one pleurisy. All included hospitalization and three patients had their treatment withdrawn as a result. There were 63 adverse events reported throughout the trial with the most common being polyuria, polydipsia and urinary tract infections.

4 | DISCUSSION

To our knowledge, the ENERGIZE trial is among the first human studies to examine the mechanisms underlying the discrepancy between the estimated and actual weight loss because of dapagliflozin treatment in a randomized, double-blind, placebo-controlled, cross-over trial. The results showed that dapagliflozin does not induce a compensatory increase in test meal food intake, nor accompanying increases in ratings of appetite across the day after short- or long-term treatment, despite reductions in body weight and liver fat. Dapagliflozin also produced no short- or long-term effects on within-meal ratings of appetite, or eating rate, energy expenditure, or brain activation in relation to food images. Taken together our data suggest that changes in appetite, food intake and energy expenditure are not the explanation for the discrepancy between the observed and anticipated weight loss during dapagliflozin treatment. It follows that other mechanisms must responsible.

Findings are consistent with those recently reported in the SEESAW study,[27] which found no change in subjectively reported measures of energy intake or appetite perceptions with empagliflozin treatment (alone or in combination with energy restricted diet) relative to placebo, in addition to no change in PYY or other appetite-related hormones (ghrelin, GLP-1).[27] Hence, data from the only two available RCTs in humans both support the notion that SGLT2i treatment is not associated with a compensatory increase in energy intake, changes in appetite, or in central (ENERGIZE) or peripheral (SEESAW) drivers of eating behaviour.

In contrast, the results of both studies are discordant with those from mathematical modelling studies, which have suggested compensatory increases in energy intake with SGLT2i. These studies, however, used a different retrospective study design to conduct hypothetical modelling based on a series of assumptions. Polidori et al. calculated that weight loss because of SGLT2i results in an increase in energy intake of approximately 100 kcal/day/kg of lost body weight, a three-fold increase compared with corresponding energy expenditure adaptations.[28] Ferrannini et al. modelled responses in patients with T2D who received empagliflozin 25 mg/day over 90 weeks with measurements of body weight, estimated glomerular filtration rate and fasting plasma glucose.[29] The model indicated a 13% increase in energy intake (269 kcal/day) with a 2% increase in daily energy expenditure because of diet-induced thermogenesis, which accounted for the 70% reduction in predicted body weight losses.

Indeed, if there was any compensatory increase in humans, there may be reasons why we could not show this in the current study. First, food intake was only measured during the test meal. It is possible that subjects behaved differently outside the research laboratory, which we would not have been able to capture. To assess this, a different methodological design would have been required to capture the energy intake changes 24 h of each day throughout the study duration. However, such studies are cumbersome, expensive and would not have been practical in our setting. Second, it must be considered whether patients made a conscious effort (despite their instructions) to restrict their food intake during dapagliflozin treatment, somehow becoming aware of their treatment condition and knowing that dapagliflozin is associated with weight loss. However, given the lack of difference in subjectively reported hunger/appetite perceptions, or in brain responses to hedonic/palatable foods, it appears unlikely that there was conscious behavioural control suppressing increased appetite or hedonic attraction to foods. In addition, the observed changes in HbA1c, blood pressure and body weight, consistent with previous dapagliflozin studies, suggest that treatment compliance was not an explanation for null effects observed in the current study.

The only two secondary outcome measures, which showed a difference were RER and liver fat. RER was significantly lower after 7 days of dapagliflozin treatment compared with placebo. This indicates that short-term dapagliflozin treatment induces a shift in substrate utilization from carbohydrate to lipid metabolism and is consistent with animal data[30] and other studies in humans.[31] This difference in RER was not replicated in the long-term study period of 12 weeks. However, it is possible that after 12 weeks treatment, the participants were very close to reaching a new steady state (i.e. weight has reached a plateau), so reversion of RER towards baseline might be expected. Even the small amounts of weight loss seen in this study should result in decreased energy expenditure, so the observation that this did not change could suggest that the lower weight loss than expected was because of energy conservation rather than an increase in food intake. Further analysis using the mathematical models provided by Hall et al. might help answer this question.[21] Energy expenditure data from ENERGIZE are similar to the studies reported by Ferrannini et al. and Merovci et al., which provided insight into whole-body metabolic adaptation in SGLT2i treatment.[31,32]

The modest weight loss with dapagliflozin treatment was associated with a significant reduction in MRI-determined liver fat, although not in abdominal VAT and SAT volumes. Many previous studies and a recent meta-analysis confirm that SGLT2i can reduce liver fat, although there is much to learn, particularly on the impact of SGLT2 on liver fibrosis.[33–36] However, their potential impact in patients with non-alcoholic fatty liver disease, with or without T2D, is increasingly being recognized.[37]

It will be interesting to observe the impact of the combination of SGLT2is and GLP-1 analogues on appetite responses, energy expenditure and body composition, including liver fat/fibrosis in future mechanistic studies.[38] Both classes of drug cause weight loss, albeit through different mechanisms. The knowledge from such mechanistic studies is necessary for treatment optimization in personalized, patient-centred approaches to weight management. In addition, the link between such medications and gut microbiota requires further exploration, as pharmaceuticals can impact microbiome composition, which in turn can affect a range of physiological and metabolic outcomes. However, the only study in humans to date suggests that dapagliflozin treatment does not significantly alter gut microbiome alpha diversity or composition.[39]

In conclusion, and as expected, dapagliflozin induced an early (transient) shift to fat metabolism, and treatment of longer duration (12 weeks) reduced HbA1c, body weight and liver fat, but not SAT or VAT volumes. Despite (albeit less than expected) weight loss, dapagliflozin was not associated with any short-term or long-term compensatory increases in food intake or energy expenditure. Dapagliflozin did not influence the psychological drivers of eating behaviour such as the subjective experiences of appetite-related phenomena, and brain reactivity to food cues.

DISSEMINATION

This study was conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in compliance with the European Union Directive 2001/20/EC transposed into UK law as statutory instrument 2004 No. 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 and all subsequent amendments and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The study was approved by the NRES North-West—Liverpool Central Research Ethics Committee (14/NW/0340; protocol number UoL000987). The trial was registered with the MHRA and has been granted a Clinical Trial Authorization (CTA). The CTA reference is its EudraCT number: 2013-004264-60.

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CONFLICT OF INTEREST STATEMENT

JW has acted as a consultant, received institutional grants, and given lectures on behalf of pharmaceutical companies developing or marketing medicines used for the treatment of diabetes and obesity, specifically Alnylam, AstraZeneca, Boehringer Ingelheim, Janssen Pharmaceuticals, Lilly, Napp, Novo Nordisk, Pfizer, Rhythm Pharma, Saniona, Shionogi, Sanofi, Takeda and Ysopia. DJC has competing interests with AstraZeneca, Boehringer Ingelheim, Janssen Pharmaceuticals, Lilly and Novo Nordisk and has received educational support from Perspectum. JCGH has acted as a consultant for Boehringer Ingelheim and Novo Nordisk. CAR has acted as a consultant for Boehringer Ingelheim. Dr Schwab reports grant and/or research support from ResMed, Inspire, and CryOSA, royalties from UpToDate and Merck Manual, research consulting for Eli Lilly, and is on the Medical Advisory Board for eXciteOSA. Other authors have no competing interests.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15257.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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