SGLT2 inhibitor dapagliflozin increases skeletal muscle and brain fatty acid in subjects with type 2 diabetes - a positron emission tomography study

Running title: Effects of dapagliflozin on fatty acid uptake

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Twitter Summary

A positron emission tomography study shows SGLT2 inhibitor dapagliflozin enhances fatty acid uptake in skeletal muscle and the brain in subjects with type 2 diabetes, extending previous findings from the liver and adipose tissue

Abstract

Objective: The aim of this study was to investigate the impact of dapagliflozin on tissue free fatty acid (FFA) uptake in skeletal muscle, the brain, small intestine, and subcutaneous and visceral adipose tissue in subjects with type 2 diabetes by using positron emission tomography (PET).

Research Design and Methods: In a 6-week randomized, double-blinded, placebo-controlled trial, 53 subjects with inadequately controlled type 2 diabetes received either dapagliflozin 10 mg or placebo daily. Tissue FFA uptake was quantified at baseline and at the end-of-treatment with PET and the long-chain fatty acid analogue tracer [^{18}F]-6-thia-heptadecanoic acid ([^{18}F]-FTHA). Treatment effects were analyzed using ANCOVA, and the results are reported as least square means and 95 % confidence intervals for the difference between groups.

Results: 38 subjects (dapagliflozin *N*=21, placebo *N*=17) completed the study. After 6 weeks, skeletal muscle FFA uptake enhanced (1.0 [0.07, 2.0] μmol*100 g^{-1}*min^{-1}, *P*=.032), whereas uptake increased only slightly in the small intestine (*P*=.09), and remained unchanged in adipose tissue. Brain [^{18}F]-FTHA uptake was also significantly increased in several regions, likely explained in part by increased FFA uptake.

Conclusions: Here we show that 6 weeks of treatment with dapagliflozin increases skeletal muscle and brain fatty acid uptake, partly driven by a rise in FFA availability. This is in line with previous hypotheses and indirect measurements showing enhanced fatty acid metabolism in response to SGLT2 inhibitor treatment, and demonstrate how widespread the shift from glucose to fatty acid utilization is at several tissues.

Article Highlights

- Why did we undertake this study? We aimed to characterize how extensive the effects of dapagliflozin were on tissue-specific fatty acid metabolism in humans.
- What is the specific question(s) we wanted to answer? We were interested to see which tissues contributed to the increased whole-body fatty acid consumption during SGLT2 inhibitor treatment.
- What did we find? We discovered that free fatty acid uptake was increased in skeletal muscle and to a modest degree in the small intestine, while the uptake of fatty acids or their derivatives was also significantly increased in the brain.
- What are the implications of our findings? As SGLT2 inhibitor treatment also reduces body fat, our study suggests that fatty acid uptake and oxidation are enhanced by dapagliflozin in several different tissues. In the brain this change is more likely a sign of improved myelin and membrane synthesis.

While sodium-glucose transporter 2 (SGLT2) inhibitors affect circulating glucose levels directly by suppressing renal glucose reabsorption in renal proximal tubules,(1) they have also been shown to induce an extensive remodeling of whole-body metabolism. Most notably, the group of drugs have been thought to enhance the use of fatty acids and ketone bodies as fuels at the expense of glucose utilization.

This hypothesis has been validated through studies using indirect calorimetry, in which treatment with SGLT2 inhibitors has indeed increased whole body lipolysis, lipid oxidation and ketogenesis.(2,3) On a tissue level, this has been studied by using positron emission tomography (PET). We have previously reported that six weeks of treatment with dapagliflozin increases hepatic, but not myocardial, free fatty acid (FFA) uptake measured with PET and the long-chain fatty acid analogue 14(*R,S*)-[^{18}F]fluoro-6-thia-heptadecanoic acid ([^{18}F]FTHA).(4,5) [^{18}F]FTHA undergoes the initial steps of β-oxidation, but the sulfur-substitution at the sixth carbon inhibits its full degradation.(5) Consequently, only 30–36 % of the [^{18}F] from FTHA enters the mitochondria in the liver, skeletal muscle and the brain, while the majority is incorporated into triacylglycerols (TAGs) and phospholipids.(6–8) Although most of the [^{18}F]-label at the C-14 is trapped intracellularly, [^{18}F]-containing compounds, such as TAGs, become present in circulation as early as 10–20 minutes after injection, with the portion of intact [^{18}F]FTHA being low (5–20 %) after 30 minutes.(6,9)

Two prior studies have used [^{11}C]-palmitate, a tracer used to characterize fatty acid oxidation in addition to uptake rate,(10) to explore the effects of SGLT2 inhibitors in humans. Similar to our findings, empagliflozin did not affect myocardial FFA uptake or oxidation when accounting for elevated serum FFA concentrations following treatment, whereas both measures decreased if only tracer transfer rates were studied.(11) An extension of the first publication reported increased FFA uptake in the visceral, but not subcutaneous, adipose tissue. However, as tracer uptake rates were not reported, it is challenging to evaluate the effect of increased serum FFA levels on the results.(12)

Here, we aimed to add to the previous findings by investigating the effects of dapagliflozin on skeletal muscle, adipose tissue, intestinal and brain FFA uptake by using [^{18}F]FTHA. We hypothesized that the treatment would be associated with enhanced skeletal muscle FFA uptake.

RESEARCH DESIGN AND METHODS

Study design

The study was a double-blind, randomized, parallel-group study focusing on the functional and metabolic changes dapagliflozin treatment induces in the myocardium (NCT03387683), with tissue fatty acid metabolism being studied in other tissues as exploratory endpoints. The study was conducted in Turku PET Centre, Turku University Hospital, Turku, Finland, and in Uppsala University Hospital, Uppsala, Sweden, from February 2018 to March 2019.

The study comprised of three visits: a screening visit 1 to 21 days before first PET study visits, a baseline PET study visit and an end-of treatment visit 6 weeks after the first PET study visit. On the second visit the subjects were randomized in a 1:1 ratio to receive either dapagliflozin 10 mg or placebo daily. The randomization was performed in blocks of two without stratification, with the scheme generated by Parexel (Parexel International, Durham, NC,

USA). Randomization was performed by a central telephone service. Compliance was evaluated based on the amount of returned study medicine.

All study procedures, PET data analyses and laboratory analyses were performed by investigators blinded to the treatment.

The study protocol was approved by Finnish Medicines Agency Fimea, the Independent Ethics Committee in Southwest Finland Hospital District and by the Regional Ethics Committee in Uppsala, Sweden. The study was conducted according to the principles of the Declaration of Helsinki. All subjects gave written informed consent prior to any study procedures.

Study subjects

A total of 53 subjects were recruited for the original study, and 38 subjects (*N*=21 dapagliflozin and *N*=17 placebo treatment arm) underwent the entire study protocol including also the [^{18}F]FTHA studies. 28 of the subjects were studied in Turku, Finland and in Uppsala, Sweden.

The subjects were required to have been previously diagnosed with type 2 diabetes based on the American Diabetes Association 2017 criteria for at least 6 months prior to the study, and to have a stable dose treatment with metformin for a minimum of 6 weeks. On the screening visit their HbA_{1c} was to be 6.0%–9.0% (42–75 mmol*mol^{-1}), BMI ≥ 25 kg*(m^2)$^{-1}$, and age 40–75 years.

Subjects were excluded if they had any other concomitant diabetes medications, uncontrolled hypertension (160/100 mmHg measured at screening), uncontrolled coronary artery disease, heart failure or arrhythmias, estimated glomerular filtration rate (eGFR) of less than 45 mL*min^{-1}*(1.73m^2)$^{-1}$, unstable or rapidly progressing renal disease or severe hepatic impairment (Child-Pugh class C).

[^{18}F]FTHA-PET/CT protocol

The PET/CT studies were conducted after a minimum of 6–8 hours of fasting, and at the end-of-treatment visit 4–6 hours after last dose of study drug, and a minimum of 12 hours after taking any other medications. A negative pregnancy test result performed on site was required from all female participants in childbearing age.

Before the PET scan, a venous catheter was inserted to either forearm and used for blood sampling and tracer administration. The dose of [^{18}F]FTHA was based on body weight, with the target of 2 MBq*kg^{-1}. Right after tracer bolus injection, a 32 min dynamic scan was started from the thoracic area (12×15 sec, 4×30 sec, 2×120 sec, 1×180 sec, 4×300 sec), followed by static frames from upper abdomen, lower abdomen and the brain, 10 minutes each. Image acquisition was performed on three GE Healthcare Discovery MI PET/CT scanners, one GE Healthcare Discovery 690 PET/CT and one GE Healthcare Sigma PET/MR (GE Healthcare, Milwaukee, WI, USA). Subjects were investigated with the same scanner at baseline and end-of study. Image data were reconstructed using iterative reconstruction (3 iterations, 16 subsets, 5 mm post filter).

PET data analysis

All PET data were corrected for dead time, decay and photon attenuation based on a low-dose CT. Tracer uptake into tissues was assessed from frames 10–32 minutes from injection by drawing free-hand volumes of interest (VOIs) with Carimas software version 2.10.(13) Paraspinal muscles were used for skeletal muscle analyses, duodenal wall was chosen to

represent the small intestine, and a mean of several VOIs drawn in subcutaneous and intraperitoneal visceral adipose tissue were used for adipose tissue analysis. For the brain the segmentation was performed by normalizing the data to an in-house template.

To obtain the rate of tissue tracer uptake with respect to tracer available in the circulation, tissue fractional [^{18}F]FTHA uptake rate (FUR, ml*[ml*min]$^{-1}$) was calculated by dividing tissue accumulated activity measured from the images by the integral of plasma activity from injection to the midpoint of the selected PET frame.(14,15) As [^{18}F]FTHA FUR is considered to express a fraction of total FFA uptake, tissue FFA uptake was calculated by multiplying FUR by serum free fatty acid concentration during the scan, and divided by tissue density, which produces the unit μmol*100 g^{-1}*min^{-1}. Whole-body [^{18}F]FTHA clearance was calculated by dividing the injected dose with plasma radioactivity area under curve from injection to extrapolated infinity.(6)

As [^{18}F]FTHA is metabolized rapidly, plasma input was corrected by measuring the remaining intact fraction of the tracer at 5, 10, 20 and 30 min from injection by using high-performance liquid chromatography, and the input curve was forced to zero after 30 minutes based on previous studies showing only diminutive amount of unmetabolized [^{18}F]FTHA after this timepoint.(16) Serum free fatty acids were measured 5 min before injection and at 32 minutes into the scan.

Laboratory measurements

Fasting plasma glucose was analyzed by hexokinase enzymatic method (Roche Diagnostics, Indianapolis, IN, USA), HbA1c with ion-exchange high-performance liquid chromatography (Bio-Rad, Hercules, CA, USA), and IFCC HbA1c was calculated using the formula IFCC = (NGSP-2.15) * 0.09148^{-1}. Enzymatic colorimetric assays were used for serum free fatty acids (WAKO Chemicals, Richmond, VA, USA with the Roche Modular and Cobas Analyzer), plasma β-hydroxybutyrate (LiquiColor, Stanbio Laboratory, Boerne, TX, USA) and plasma lactate (Roche Diagnostics).

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp, Armonk, NY, USA). Distribution of the data was evaluated with Shapiro-Wilk test, and logarithmic transformation was performed on non-normally distributed parameters (HbA_{1c}, daily dose of metformin). Baseline differences between groups were evaluated with independent samples *t* test, or Mann-Whitney U-test for non-normally distributed data (β-hydroxybutyrate). Changes in anthropometric measurements, laboratory tests, and tissue fractional [^{18}F]FTHA uptake and FFA uptake rates were analyzed using ANCOVA with treatment group as the independent variable and baseline values as covariates. For the brain, a similar statistical analysis was used with statistical parametric mapping.(17) Associations between changes in laboratory results and fractional tracer uptake were studied using Pearson correlation. Baseline results are reported as means and SDs, and treatment effects as least square means with 95 % confidence interval for the difference between groups. For β-hydroxybutyrate, value 0.09 μmol/L was used for the subjects with result below the measurement range (below 0.1 μmol/L). A per protocol analysis using the complete data (N=38) was done.

RESULTS

Subject characteristics

Baseline characteristics of both treatment arms are reported in Table 1. There were no significant differences between groups concerning sex distribution, age, BMI, glycaemia, or time since diagnosis, with all the subjects being Caucasian. The daily doses of metformin ranged from 500 mg to 3000 mg similarly in both groups. Compliance was 95 % or higher in both treatment arms, and no side effects were reported.

Effects of dapagliflozin on weight and circulating metabolites

In the dapagliflozin group, there were significant reductions in weight, BMI, fasting plasma glucose and HbA_{1c} after 6 weeks of treatment compared to placebo. Serum fasting β-hydroxybutyrate levels increased, whereas there was no difference in fasting lactate concentrations, or levels of serum free fatty acid concentrations during the scan (Table 1).

Changes in peripheral FFA uptake

There were no significant differences in tissue [^{18}F]FTHA fractional uptake rate (FUR) or FFA uptake between treatment arms at baseline (Table 2). Dapagliflozin treatment was associated with a significant increase in liver [^{18}F]FTHA FUR, while the treatment effect was also significant in the skeletal muscle when accounting for the levels of circulating FFAs. In duodenum, despite a similar percentual increase from baseline as in skeletal muscle, the increases in [^{18}F]FTHA FUR and FFA uptake did not reach statistical significance (Table 2 and Figure 1.)

Except for a modest negative correlation between a decrease in plasma glucose and an increase in hepatic [^{18}F]FTHA FUR and FFA uptake (N=17, r=-0.49, P=.045 and r=-0.48, P=.045, respectively), changes in serum FFA levels, plasma β-hydroxybutyrate, lactate or glucagon/insulin-ratio were not correlated with the changes in tissue fatty acid metabolism in any organ in the dapagliflozin group. Accordingly, no direct association between tissue [^{18}F]FTHA FUR and circulating substrate levels or glucagon/insulin-ratio were observed at baseline in the whole study group.

Increased brain tracer uptake

Brain [^{18}F]FTHA FUR and FFA uptake were increased globally, with no significant differences between different anatomical brain regions (Table 2 and Figure 2).

Interestingly, brain fractional uptake rate of [^{18}F]FTHA was significantly correlated with that in the liver and duodenum at baseline in the whole group (N=38, r=0.51, P=.001 and r=0.59, P<.001, respectively). In the dapagliflozin treatment arm, the increase in brain [^{18}F]FTHA fractional uptake rate was also correlated with the [^{18}F]FTHA FUR changes in the liver and duodenum (N=20, r=0.64, P=.003 and r=0.74, P <.001, respectively). In comparison, no similar association could be found between the brain and skeletal muscle or adipose tissue (P values >0.6) (Supplemental Figure 1).

No significant effects on [^{18}F]FTHA plasma metabolites or clearance

Ratios of unmetabolized [^{18}F]FTHA to total plasma activity were similar between groups at baseline, averaging 88.6 % (SD 6.3) at 5 min, 69.3 % (SD 11.3) at 10 min, 42.6 % (SD 10.1) at 20 min and 27.2 % (SD 6.8 %) at 30 min after tracer injection. The ratios were not affected by dapagliflozin (*P* values >.2 at each time point). In both groups and on both visits the decline in radioactivity in plasma evened after 20 minutes signalling an increase in circulating metabolites of [^{18}F]FTHA.

CONCLUSIONS

This is the first study to report the effects of SGLT2 inhibitor dapagliflozin on tissue-specific fatty acid uptake in skeletal muscle, small intestine and the brain in humans *in vivo*. The findings are well in line with previous hypotheses of a wide-spread substrate-shift from glucose to fatty acids, as well as prior studies showing enhanced fatty acid β-oxidation in response to SGLT2 inhibitor treatment in the whole body and *in vitro*.(18,19)

In skeletal muscle, the increase in FFA uptake is partly accounted for by the increase in serum FFAs, as the increase in [^{18}F]FTHA uptake (i.e. before accounting for the concentrations of circulating FFA) did not reach statistical significance. The mean 22 % increase in skeletal muscle FFA is slightly higher than the 15–20 % increase in daytime whole-body oxidation reported by Op den Kamp et al.(3), and might therefore support the findings that SGLT2 inhibitor treatment not only enhances β-oxidation,(18) but also increases intramyocellular lipid content in muscle cells.(20) This paradoxical increase in lipid content has previously been linked to improved metabolic health when observed simultaneously with enhanced mitochondrial function in response to physical exercise (21), so it is less likely to be a deleterious effect.

Despite the small intestine being a significant producer of TAGs from dietary fats, plasma FFAs are mainly used as sources of energy or for the build-up of phospholipids in enterocytes.(22) In the present study, the rate of intestinal FFA uptake in the subjects was similar to those with severe obesity in a previous study and elevated in comparison to healthy controls,(23) with the increased availability of plasma FFAs also possibly contributing to the results.

We did not observe changes in visceral or subcutaneous adipose tissue FFA uptake, which is in line with several previous reports showing significant decrease in adipose tissue volume in both depots.(24) This is in contrast to Lauritsen et al.,(12) who have reported increased fatty acid uptake in the visceral, but not subcutaneous adipose tissue after 4 weeks of treatment with empagliflozin. As GLUT4 expression was also decreased possibly hindering glycerol production and lipid storage in white adipocytes, the authors attributed this finding to increased lipid turnover in visceral adipose tissue and increased FFA availability. Of important note, a different radiotracer [^{11}C]-palmitate, was used, and thus the direct comparison may not be feasible and could explain the apparently discrepant results.

The most surprising finding was the 30 % increase in brain [^{18}F]FTHA and FFA uptake. In the whole study group, baseline FFA uptake rates in white and grey matter were similar to subjects with severe obesity, equalling a 2–3 fold higher rate compared to healthy, lean controls.(7) While the final fate of fatty acids taken up by the brain remains debatable, the majority of FFAs are likely stored as lipids rather than consumed as fuels. This is supported by a previous study reporting that more than 69 % of [^{18}F]FTHA total radioactivity was recovered in the brain lipid

pool, mostly as TAGs (53 %) and phosholipids (7 %).(7) Moreover, the capacity of the brain to oxidize fatty acids has been considered limited in order to restrain oxidative stress,(25) and the total amount of oxygen that would be needed for the complete oxidation of the measured FFA uptake would largely exceed the actual brain oxygen consumption(26).

Still, it has been suggested that the brain might be able to oxidize up to 20 % of the fatty acids it stores.(27) Therefore, it is also possible that the current finding is to some extent a sign of improved brain mitochondrial oxidative capacity. Nevertheless, as cognitive function has been shown to improve in response to SGLT2 inhibitor treatment in several animal models,(28) it seems unlikely that the production of reactive oxygen species would increase. Therefor it can be hypothesized that the increased need for fatty acid compounds in the brain acids originates from enhanced myelination in the white matter and attenuated rate of membrane turnover in the gray matter, both of which have been shown to impede in type 2 diabetes.(29,30)

Another interesting finding of our study is the association between the brain and liver and small intestine [^{18}F]FTHA uptake. Considering that liver and intestine are the main TAG producers in the body, the brain readily takes up TAGs(31), and [^{18}F]FTHA is known to swiftly incorporate into TAGs,(6) it is possible that the tracer is circulated rapidly to the brain, scanned 52–62 minutes after injection, and 20–30 minutes later than the peripheral tissues. This would be in line with the previously suggested upregulated fatty acid turnover in response to SGLT2 inhibitor treatment (12). However, as total plasma radioactivity remained rather low, below 6 % from maximum, from 15 minutes post injection onwards, the most significant part of the signal likely represents increased free fatty acid uptake in the brain.

Unfortunately brain fatty acid and [^{18}F]FTHA uptake are still inadequately understood to fully elucidate the current findings(32), limiting the interpretation of the results. For one, we did not measure [^{18}F]-containing compounds in TAGs, nor the change in cholesterol levels during the treatment. Furthermore, while several different metabolites of [^{18}F]FTHA are known to exist, they have not been characterized in detail, so there might be currently unknown intermediates interfering with the brain result. Based on current knowledge, [^{18}F]FTHA should not significantly degrade to [^{18}F] carrying ketone bodies(33), so ketonemia associated with SGLT2 inhibitor treatment should not explain the result. As all the peripheral tissues were analysed from scans performed within 30 minutes from injection, the results are more likely to correctly represent free fatty acid uptake in these tissues, although the contribution of other tracer metabolites cannot be completely excluded. The duration of the study was also rather short, so it might be that the observed changes do not persist in a more chronic setting. Finally, future studies that simultaneously assess brain FFA uptake and cognitive function, would be highly informative.

To conclude, we show that 6 weeks of treatment dapagliflozin induces a significant increase in skeletal muscle and brain fatty acid uptake in subjects with type 2 diabetes by using direct *in vivo* metabolic imaging. We hypothesize that these changes mirror different tissue-specific changes in response to SGLT2 inhibitor treatment: increased uptake in response to abundant circulating FFAs in skeletal muscle; the enhanced capacity to use free fatty acids as fuels via β-oxidation in the skeletal muscle, liver and intestines; upregulated cholesterol synthesis in the liver and intestines; and enhanced myelination and membrane turnover in the brain. Further studies on the effects of SGLT2 inhibitors on tissue metabolism are however warranted, especially concerning the changes in the central nervous system, to further characterize the changes in free fatty acid utilization in the brain.

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Conflict of Interest. K.H. is an employee of Antaros Medical and J.O. is employed by AstraZeneca Gothenburg. Other authors report no potential conflicts of interest.

Author Contributions and Guarantor Statement. A.L-R., E.R. and S.L performed the study visits. A.L-R., J.T., A.B., H.K., J.K. and K.H. performed PET data analyses. A.K.K. is accounted for [^{18}F]-FTHA production and R.A. for tracer metabolite analysis. A.L-R., E.R., S.L., J.O. and P.N. participated in study planning. A.L.-R. and J.T. performed the statistical analyses. All authors commented on initial version of the manuscript. P.N. is the principal investigator and guarantor 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.

Prior Presentation. Part of the results have been previously presented on 4th of October 2023 in the 59th Annual Meeting of the European Association for the Study of Diabetes in Hamburg, Germany, with the title "SGLT2 Inhibitor Dapagliflozin Increases Skeletal Muscle and Brain Fatty Acid Uptake in Subjects with Type 2 Diabetes - A Positron Emission Tomography Study".

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TABLES

	Baseline			End-of-treatment		
	Dapagliflozin *N* = 21	Placebo *N* = 17	Sig.	Mean difference	95 % CI	Sig.
Age (years)	64 ± 8	66 ± 6	.32			
Sex (M/F)	15/6	8/9	.19			
Time since diagnosis (years)	6.3 ± 4.4	8.6 ± 6.8	.28			
Metformin dose (mg)	1345 ± 768	1294 ± 830	.69			
BMI ($kg*m^{-2}$)	30.4 ± 3.6	28.9 ± 3.0	.17	-0.5	[-0.7, -0.2]	<.001***
Glucose (mmol/L)	7.7 ± 1.3	7.5 ± 1.35	.70	-0.63	[-1.0, -0.2]	.003**
GHbA1c (%)	6.7 ± 0.49	6.6 ± 0.71	.64	-0.2	[-0.3, -0.1]	.009**
HbA1c (mmol/mol)	49.7 ± 5.2	48.5 ± 7.8	.60	-2.2	[-3.8, -0.7]	.006**
β-hydroxybutyrate (µmol/L)	0.13 ± 0.06	0.21 ± 0.14	.02*	0.27	[0.03, 0.51]	.03*
FFA mean (mmol/L)	0.79 ± 0.21	0.78 ± 0.25	.83	0.06	[-0.05, 0.18]	.27
Lactate (mmol/L)	1.50 ± 0.57	1.34 ± 0.45	.34	-0.17	[-0.37, 0.04]	.11
Insulin (pmol/L)	55.4 ± 24.9	55.7 ± 31.1	.18	-8.1	[-21.7, 5.5]	.24
Glucagon (pmol/L)	13.4 ± 8.4	13.7 ± 7.8	.90	0.4	[-2.1, 2.9]	.75
Insulin/glucagon ratio	5.1 ± 3.0	4.1 ± 3.0	.28	-0.4	[-1.4, 0.6]	.45

Table 1. Baseline characteristics of the two groups, and the effects of treatment on anthropometric and laboratory measures compared to placebo. Baseline data are expressed as mean ± SD and treatment effects as means and 95 % Cis for difference.

	Baseline			End-of-treatment		
	Dapagliflozin	Placebo	Sig.	Mean difference	95 % CI for difference	Sig.
[^{18}F]-FTHA fractional uptake rate (ml*[ml*min]$^{-1}$ *1000)						
Skeletal muscle	6.47 ± 1.48	7.49 ± 1.85	0.07	0.58	[-0.26, 1.43]	.17
Duodenum	30.71 ± 9.83	32.88 ± 9.73	0.50	5.35	[-0.37, 11.06]	.07
Liver	206.6 ± 45.9	215.8 ± 43.8	0.55	35.0	[13.2, 57.4]	.003**
Visceral AT	4.53 ± 1.15	5.66 ± 2.35	0.08	0.54	[-0.43, 1.50]	.27
Subcutaneous AT	3.16 ± 0.71	3.54 ± 0.76	0.13	0.25	[-0.22, 0.72]	.29
White matter	8.56 ± 2.10	9.21 ± 1.02	0.27	1.31	[0.48, 2.14]	.003**
Gray matter	7.60 ± 1.90	8.24 ± 1.36	0.34	1.26	[0.35, 2.17]	.008**
Whole brain	7.25 ± 1.68	7.71 ± 0.96	0.34	1.12	[0.41, 1.84]	.003**
FFA uptake rate (µmol*100 g^{-1}*min^{-1})						
Skeletal muscle	0.49 ± 0.16	0.56 ± 0.22	0.24	0.11	[0.01, 0.20]	.03*
Duodenum	2.37 ± 1.17	2.47 ± 1.12	0.79	0.59	[-0.10, 1.28]	.09
Liver	15.46 ± 5.40	16.32 ± 6.69	0.67	4.51	[0.80, 8.21]	.02*
Visceral AT	0.39 ± 0.16	0.46 ± 0.24	0.29	0.09	[-0.04, 0.22]	.30
Subcutaneous AT	0.27 ± 0.09	0.29 ± 0.10	0.43	0.04	[-0.04, 0.11]	.15
White matter	0.41 ± 0.13	0.46 ± 0.14	0.26	0.11	[0.03, 0.20]	.01*
Gray matter	0.37 ± 0.13	0.41 ± 0.13	0.30	0.10	[0.02, 0.18]	.01*
Whole brain	0.35 ± 0.11	0.39 ± 0.11	0.34	0.10	[0.02, 0.17]	.01*

Table 2. Tissue [^{18}F]-FTHA fractional uptake and FFA uptake rates at baseline and the mean differences in change from baseline to end-of-treatment compared to placebo. Baseline data are expressed as mean ± SD and treatment effects as means and 95 % CIs for difference between groups. AT adipose tissue, FFA free fatty acid.

Figures

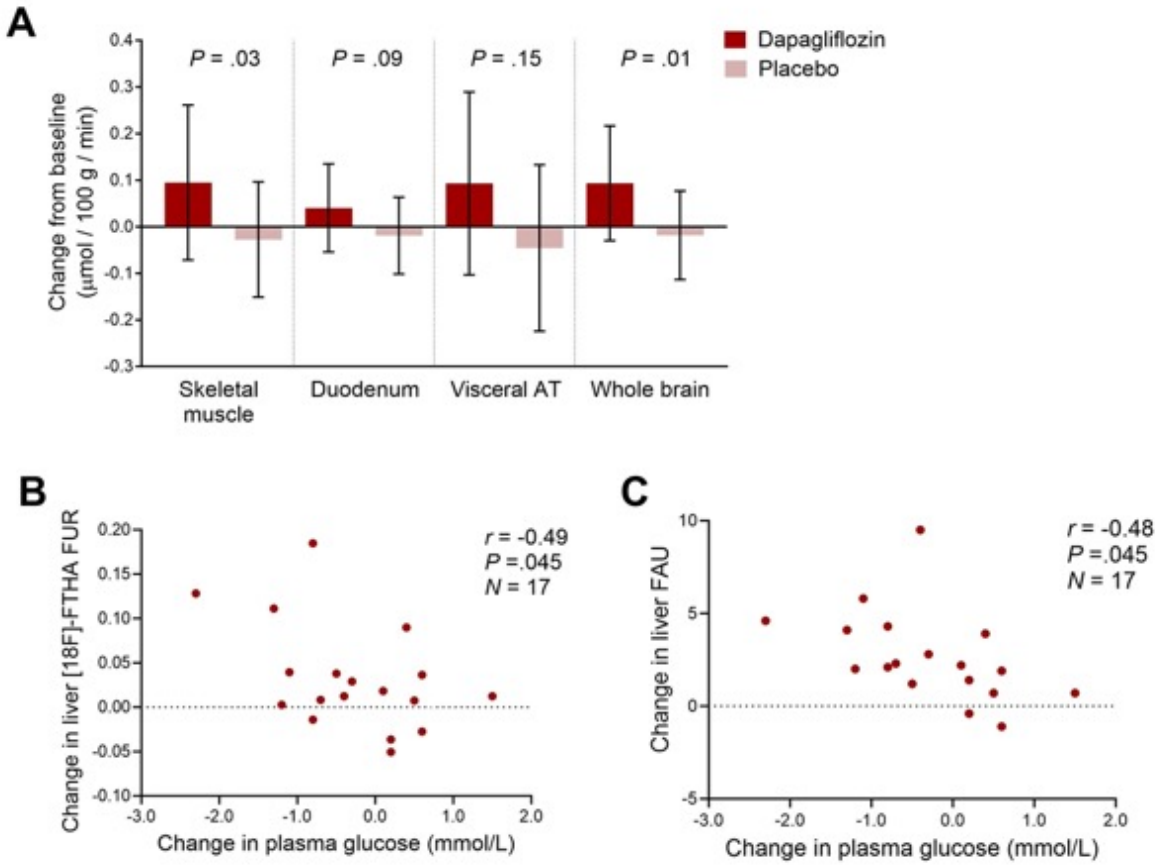


Figure 1. A. Dapagliflozin enhanced skeletal muscle and brain fatty acid uptake, whereas the changes were not statistically significant in the small intestine or visceral adipose tissue. B. and C. A more pronounced treatment-induced decrease in plasma glucose level was associated with a more significant increase in hepatic [18F]FTHA fractional uptake rate and free fatty acid uptake. AT, adipose tissue, FAU fatty acid uptake (µmol*100 g-1*min-1), FUR fractional uptake rate (ml/[ml*min] -1).

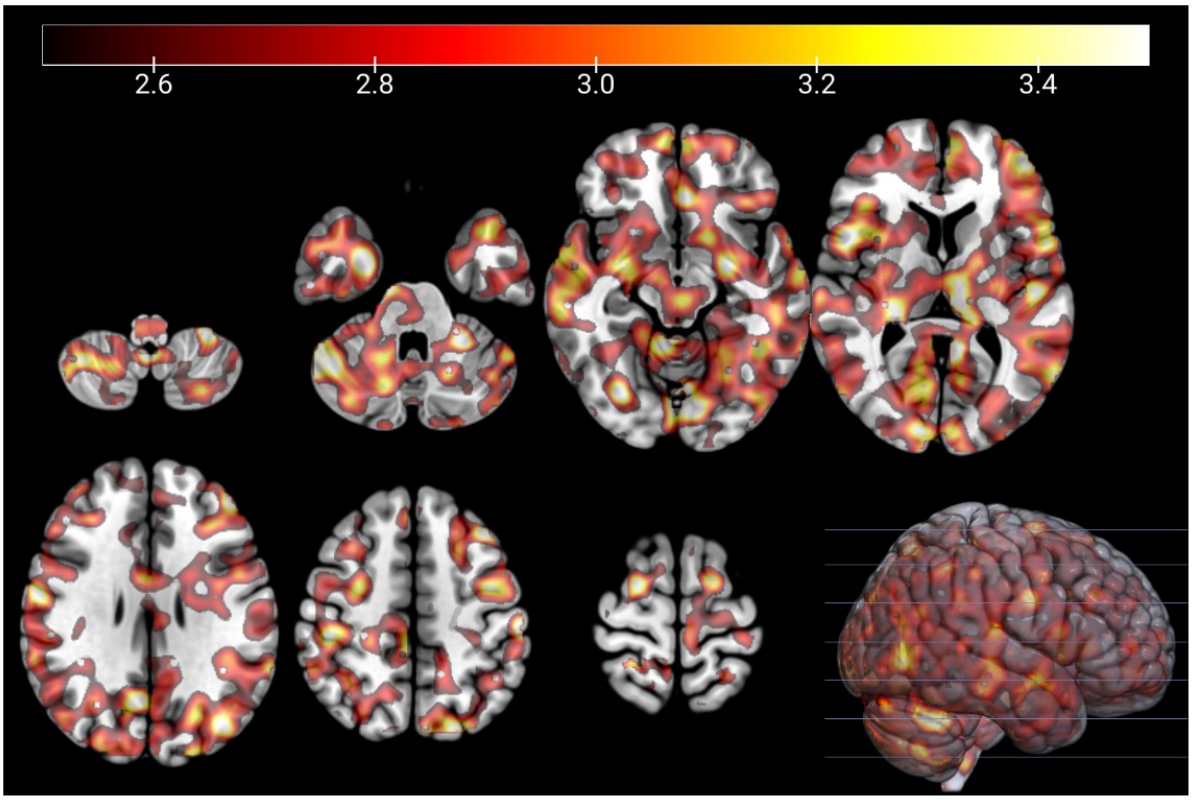
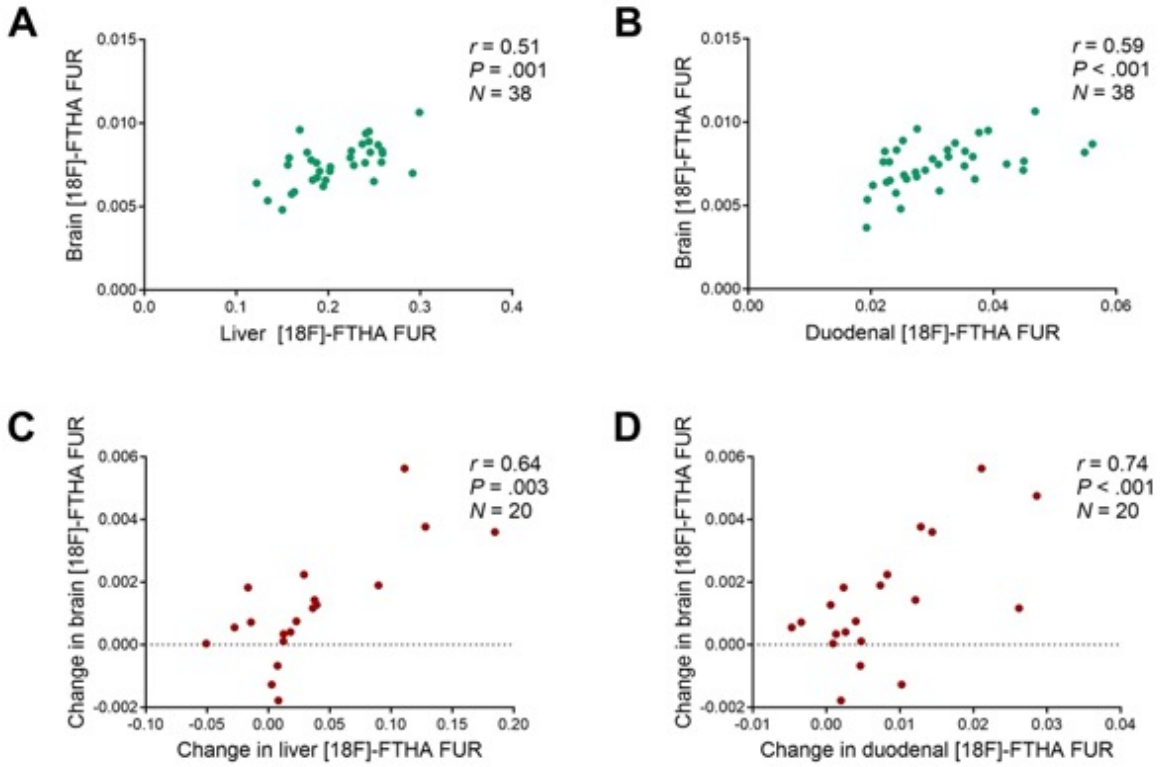


Figure 2. Brain [18F]FTHA fractional uptake rate was increased globally and more distinctively in cortical areas. Brighter color indicates a higher T-score, and a more significant difference between treatment arms.



Supplemental Figure 1. Brain [18F]FTHA fractional uptake correlated with hepatic and intestinal [18F]FTHA fractional uptakes, whereas there was no association with skeletal muscle.