Emilia Lankinen

THE EFFECT OF SGLT2-INHIBITOR DAPAGLIFLOZIN ON THE FATTY ACID METABOLISM OF THE KIDNEYS AND THE RENAL SINUS FAT: A RANDOMIZED, PLACEBO-CONTROLLED STUDY

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Dapagliflozin is an SGLT2-inhibitor that is used in the treatment of type 2 diabetes. This class of drugs have renal and cardiometabolic benefits, including reducing visceral fat, lowering blood pressure and modulating whole body metabolism. The aim of our study was to see how dapagliflozin affects fatty acid metabolism of the kidneys, and see if dapagliflozin reduces renal sinus fat, which has been hypothesized to be the mechanism through which SGLT2-inhibitors lower blood pressure.

Our data has been collected from two different randomized, placebo-controlled studies: DERISC and DAPAKID. Participants were given either dapagliflozin 10 mg or placebo. Participants underwent imaging at the beginning and end of the experiment. Renal sinus fat was measured from MRI-images using Carimas-software. Renal fatty acid uptake was measured with FTHA-radiotracer from PET/CT-imaging.

At the end of treatment, renal sinus fat had decreased in the left kidney in the dapagliflozin treatment group. No change was seen between groups on the right side. A negative correlation was seen between HbA1c and change in renal sinus fat in the left kidney. We did not see a significant effect on renal fatty acid uptake.

In conclusion, our results showed that a short intervention with dapagliflozin affects the volume of renal sinus fat modestly but is unlikely the reason for the renal and cardiometabolic benefits associated with SGLT2-inhibitors. In contrast to previous research on other tissues, dapagliflozin did not alter renal fatty acid uptake significantly.

Avainsanat: dapagliflotsiini, SGLT2-estäjä, munuaisrasva, rasvahappometabolia

The Effect of SGLT2-inhibitor Dapagliflozin on the Fatty Acid Metabolism of the Kidneys and the Renal Sinus Fat: a Randomized, Placebo-controlled Study

Emilia Lankinen[1], Eleni Rebelos[1,2] (ORCID 0000-0003-3050-8692), Sanna Laurila[1,3] (ORCID 0000-0002-1170-5079), Laura Pekkarinen[1] (ORCID 0000-0002-5596-0485), Henrik Isackson[4,5] (ORCID 0000-0002-0036-1979), Richard Aarnio[6] (ORCID 0000-0002-6420-514X), Kerstin Heurling[7], Jonas Oldgren[4,8] (ORCID 0000-0002-9969-392), Jan Oscarsson[9] (ORCID 0000-0002-4573-517X), Pirjo Nuutila[1,10] (ORCID 0000-0001-9597-338X), Aino Latva-Rasku[1,10] (ORCID 0000-0001-8786-9160)

[1]Turku PET Centre, University of Turku, Turku, Finland
[2]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[3]Heart Center, Turku University Hospital, Turku, Finland.
[4]Clinical Physiology and Cardiology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden.
[5]Integrative Physiology, Medical Cell Biology, Uppsala University Hospital, Uppsala, Sweden.
[6]Radiopharmaceutical Chemistry Laboratory, Turku PET Centre, University of Turku, Turku, Finland.
[7]Antaros Medical AB, Gothenburg, Sweden.
[8]Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden.
[9]Late-Stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals Research and Development, AstraZeneca, Gothenburg, Sweden.
[10]Department of Endocrinology, Turku University Hospital, Turku, Finland.

Corresponding author:

Aino Latva-Rasku, MD, PhD

University of Turku, Turku, Finland

address: Kiinamyllynkatu 4-8, 20520 Turku, Finland

telephone: +358407701288

e-mail address: aehyyp@utu.fi

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Abstract

Aims: The first aim of our study was to investigate how 8 weeks of dapagliflozin treatment affects the renal sinus fat of the kidneys. The second part of our investigation aimed to see how dapagliflozin affects the fatty acid uptake of the kidneys.

Methods: The data for our study has been collected from two randomized, double-blind, placebo-controlled studies. In the DERISC study, patients were randomized to receiving 10 mg dapagliflozin or placebo for 8 weeks, and whole-body MRI-imaging was performed at baseline and at the end of treatment. In the DAPAKID study, participants received either 10 mg dapagliflozin (N=21) or placebo (N=17) for 6 weeks, and tissue fatty acid uptake was measured with positron emission tomography using 14(R,S)-[18F]fluoro-6-thia-heptadecanoic acid ([^{18}F]FTHA).

Results: At end of treatment, a statistically significant difference between treatment groups was seen for the change of RSF volume in the left kidney (p=0.03). However, on the right side there was no statistically significant difference (p=0.08). A significant negative correlation between change in HbA1c and change in RSF on the left was seen (r=-0.57, p=0.04). No other significant correlations were seen between renal sinus fat and BMI, eGFR, blood pressure or waist circumference.

Dapagliflozin does not significantly affect renal fatty acid uptake. There was no statistically significant difference between groups in kidney FUR (p=0.09). A slight positive correlation between change in kidney FUR and change in liver FTHA was seen (r=0.61, p=0.004).

Conclusions: Our results show that a short intervention with dapagliflozin affects the volume of renal sinus fat modestly, but this is unlikely the driver of the renal and cardiovascular benefits associated with the group of drugs. Additionally, in contrast to several other tissues, a short intervention with dapagliflozin did not alter renal fatty acid uptake significantly.

Trial registration: ClinicalTrials.gov NCT03387683 and NCT02426541

Keywords

Dapagliflozin, fatty acid uptake, positron emission tomography, renal sinus fat, SGLT2 inhibitors

Abbreviations

FA, fatty acid

FFA, free fatty acid

FTHA, 14(R,S)-[18F]fluoro-6-thia-heptadecanoic acid ([18F]FTHA)

PDFF, proton density fat fraction

PET, positron emission tomography

RSF, renal sinus fat

SGLT2, sodium-glucose transporter 2

WtoH, waist to hip ratio

Research in Context

- What is already known about this subject?
    - SGLT2-inhibitors modulate whole-body energy metabolism by increasing the use of fatty acids in the brain, liver and skeletal muscle
    - Renal sinus fat volume has been correlated with blood pressure
    - SGLT2-inhibitors decrease liver volume, liver fat and visceral adipose tissue volume
- What is the key question?
    - How does dapagliflozin affect renal sinus fat volume and fatty acid uptake?
- What are the new findings?
    - After 8 weeks of treatment with dapagliflozin, the amount of renal sinus fat volume decreased
    - Dapagliflozin does not significantly affect renal fatty acid uptake
- How might this impact on clinical practice in the foreseeable future?
    - Dapagliflozin reduces not only visceral adipose tissue and hepatic fat, but also renal sinus fat, which may represent an additional mechanism contributing to its renoprotective effects and blood pressure–lowering properties.

Introduction

Dapagliflozin is a highly selective inhibitor of renal sodium-glucose transporter 2 (SGLT2) and is approved for the treatment of patients with type 2 diabetes. This class of drug inhibits glucose reabsorption in the proximal tubulus of the kidneys, thus increasing glucosuria [1]. SGLT2-inhibitors have also been shown to reduce visceral fat, improve prognosis of heart failure and slow down the process of diabetic nephropathy [2,3].

It has been shown that SGLT2 inhibitors modulate whole-body energy metabolism by increasing the use of fatty acids as fuel instead of glucose. We have previously shown that dapagliflozin increases fatty acid uptake in the brain, liver and skeletal muscle [4]. However, it has not been researched how this class of drugs affects the use of fatty acids in the kidneys. Based on previous research on fatty acid uptake, we hypothesised that fatty acid uptake would enhance also in the kidneys, as it has in other tissues.

Renal sinus fat (RSF) is an ectopic fat deposit located in the hilum of the kidneys and has been linked to chronic kidney disease. RSF accumulation has been hypothesized to affect intrarenal pressure and activate the renin-angiotensin-aldosterone system and impair renal perfusion, which could all potentially lead to hypertension and chronic kidney disease [5,6]. Hypertension has been linked with a larger RSF compared to normotensive patients [7].

It has previously been shown that SGLT2 inhibitors reduce liver volume, liver proton density fat fraction (PDFF), and visceral adipose tissue volume [3]. To further investigate the effects of SGLT2 inhibitors, we examined the impact of 8 weeks of dapagliflozin treatment on renal sinus fat (RSF), as measured by whole-body MRI. We hypothesized that dapagliflozin would reduce RSF, which may represent one mechanism underlying the blood pressure–lowering effects of SGLT2 inhibitors. RSF has been associated with hypertension, and greater RSF has also been linked to lower eGFR [5,8].

Methods

Study outline

The data for this study has been collected from two randomized, double-blind, placebo-controlled studies performed at Turku PET Center, Turku, Finland. In the DERISC study (NCT02426541 [3]), 31 patients were randomized to receiving 10 mg dapagliflozin (N=15) or placebo (N=16) for 8 weeks, and whole-body MRI-imaging was performed at baseline and at the end of treatment. In the DAPAKID study (NCT03387683 [4]), participants received either 10 mg dapagliflozin (N=21) or placebo (N=17) for 6 weeks, and tissue fatty acid uptake was measured with positron emission tomography (PET) using long-chain fatty acid (FA) analog tracer 14(R,S)-[18F]fluoro-6-thia-heptadecanoic acid ([^{18}F]FTHA)[8]. The inclusion criteria was similar in both studies: patients had to have previously been diagnosed with type 2 diabetes, were between 35–75 years of age and had BMI between 25–40 kg/m^2. Patients with any other concomitant diabetes medication, other than metformin or dipeptyl peptidase 4 inhibitors, and decreased renal

function (eGFR below 60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) were excluded. All subjects gave written informed consent before any study procedures.

Measurement of RSF volumes

RSF volumes were measured from MRI data acquired on a 3T PET/MR system (Philips Ingenuity TF, Philips Healthcare, USA) during breath-hold using the integrated body coil. A 3D multi-echo water–fat gradient-echo sequence was used with TR = 5.37 ms, three unipolar echoes (TE1 = 0.99 ms, ΔTE = 1.61 ms), and a flip angle of 6°. The field of view was 502 × 340 × 152 mm^3 with an acquired voxel size of 1.96 × 1.96 × 8.0 mm^3. RSF was drawn free-handedly onto the MRI-images for participants in the DERISC study (N=23) using Carimas software (version 2.10) [9]. The rest of the participants were excluded due to inadequate imaging regarding the kidneys.

Measurement of renal fatty acid uptake

Renal cortical [^{18}F]FTHA uptake was measured under fasting conditions using cross-calibrated PET/CT scanners (GE Healthcare Discovery MI PET/CT and Discovery 690 PET/CT). PET data were corrected for dead time, decay, and photon attenuation using low-dose CT. Radiotracer uptake in the renal cortex was quantified from a static 10-min frame acquired 42–50 min after intravenous bolus administration of 150 MBq [^{18}F]FTHA. Volumes of interest were manually drawn on the renal cortex using Carimas software (version 2.10)[9]. Tissue fractional [^{18}F]FTHA uptake rate (FUR, $ml \cdot ml^{-1} \cdot min^{-1}$)[8] was calculated by dividing tissue activity measured from PET images by the integral of radiometabolite-corrected plasma radioactivity from injection to the midpoint of the selected frame.

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics for Windows (version 30.0.0.0 ; IBM Corp., Armonk, NY). A p-value of <0.05 was considered statistically significant.

Data distribution was evaluated with the Shapiro-Wilks test. Logarithmic transformation was done on non-normally distributed parameters. Baseline characteristics between groups were evaluated with independent samples *t* test or Mann-Whitney *U* test for non-normally distributed data. Treatment effects on anthropometric measurements, laboratory tests, and tissue FTHA and FFA uptake rates were analysed using ANCOVAs.

Results

Baseline characteristics

There was no difference in baseline characteristics between groups in either DAPAKID or DERISC studies ($p>0.05$). Baseline characteristics have been presented at higher detail in the original articles[3,4].

In the DERISC study, were 31 participants, 25 male and 6 female. The mean age was 61 (SD 7.8) years. 15 participants had metformin monotherapy and 16 used metformin and

sitagliptin. 17 participants had hypertension. At baseline, mean BMI was 31.9 (SD 4.4) kg/m^2. Waist circumference was 109.5 (SD 9.8) cm and waist to hip ratio (WtoH) was 0.64 (SD 0.06). Mean HbA1c was 52.0 (SD 6.5) mmol/mol.

In the DAPACARD study there were 38 participants, 23 male and 15 female. Mean age was 65 (SD 7.4) years. At baseline, mean BMI was 29.7 (SD 3.4) kg/m^{2}and HbA1c 49.2 (SD 6.4) mmol/mol.

Modest reduction in RSF after 8 weeks of treatment

There were no significant differences between groups in RSF volumes at baseline (Table 1). At end of treatment, a statistically significant difference between treatment groups was seen for the change of RSF volume in the left kidney (F[1,27]=5.07, p=0.03, 95 % CI [-5.1, 1.6]). However, on the right side there was no statistically significant difference (F[1,26]=3.26, p=0.08, 95 % CI [-4.1, 2.9]) (Figure 1).

There was a statistically significant negative correlation between change in HbA1c and change in RSF on the left (r=-0.57, p=0.04), but not on the right (r=0.47, p=0.11). There was no statistically significant correlation between change in RSF volume on the right or left side compared to change in weight, BMI, eGFR, systolic blood pressure or diastolic blood pressure (p-values >0.40). No statistically significant treatment effect was seen in change in waist circumference (p=0.08) or systolic or diastolic blood pressure (p=0.83, p=0.64, respectively).

Table 1. **Renal sinus fat volumes at baseline and end of treatment**

	Dapagliflozin 10 mg			Placebo		
	Baseline	**End of Treatment**	**Change**	**Baseline**	**End of Treatment**	**Change**
RSF volume right, ml	10.2 (SD 5.7)	9.3 (SD 5.4)	-0.8 (SD 2.0)	9.1 (SD 3.5)	9.1 (SD 3.5)	-0.2 (SD 2.0)
RSF volume left, ml	13.1 (SD 4.9)	12.2 (SD 4.8)	-0.2 (SD 2.6)	10.7 (SD 3.9)	11.1 (SD 4.3)	1.3 (SD 3.2)

Data are presented as mean (SD). RSF renal sinus fat.

No significant change in kidney fatty acid uptake

There was no statistically significant difference between groups in kidney cortex fatty acid fractional uptake rate (F[1,36]=2.97, p=0.09, 95 % CI [-0.010,0.003], Figure 1). However, there was a slight positive correlation between the changes in kidney and liver fatty acid fractional uptake rates (r=0.61, p=0.004).

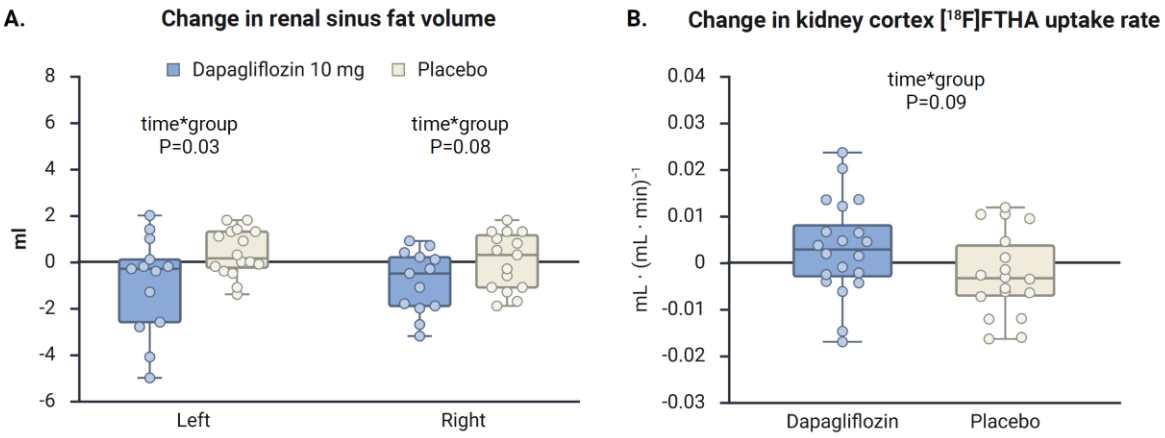

Figure 1: *A: There was a significant change in renal sinus fat volume in the left kidney compared to placebo group. B: The change in kidney FTHA uptake rate was not significant between groups.*

Discussion

Our results demonstrate that short-term dapagliflozin treatment leads to a modest reduction in renal sinus fat (RSF) volume, while having minimal impact on renal fatty acid uptake. These findings suggest that changes in RSF are unlikely to be a primary driver of the established renal and cardiovascular benefits of SGLT2 inhibitors.

The observed reduction in RSF was more confined to the left kidney, which may reflect previously reported asymmetrical fat accumulation, with greater deposition on the left side [10]. As no significant change in blood pressure was observed, the role of RSF volume in SGLT2 inhibitor–associated blood pressure reduction cannot be determined. Methodologically, the measured RSF volumes were consistent with prior reports [6,11], supporting the validity of our approach despite the relatively large voxel size and the MRI acquisition not being optimized for renal assessment.

In contrast to effects observed in other tissues, dapagliflozin did not significantly alter renal fatty acid uptake. However, there was an association between the significant increase in liver fatty acid uptake [4], suggesting a similar, but milder change in substrate use might occur in the kidney cortex.

This study has several limitations. The small sample size and short intervention period restrict the ability to detect more subtle or long-term effects. Due to the small sample size and technical limitations of MRI, variability was high. Larger and longer-duration studies are warranted to further clarify the role of RSF in the renal actions of dapagliflozin.

Despite these limitations, our findings provide novel insight into the renal effects of dapagliflozin. Specifically, the observed reduction in renal sinus fat volume, together with minimal changes in renal fatty acid uptake, suggests that dapagliflozin may exert subtle, tissue-specific effects on renal fat distribution and metabolism. While these changes are unlikely to represent primary mechanisms underlying its cardiorenal benefits, they highlight potentially relevant pathways that warrant further investigation.

Data availability

The data that support the findings of this study are available from the corresponding author, A.L.-R. upon reasonable request.

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Duality of Interest.

K.H. is an employee of Antaros Medical. J.Os. is employed by AstraZeneca AB. No other potential conflicts of interest relevant to this article were reported.

Contribution statement

E.L., E.R., K.H. and A.L.-R. performed the data analyses. E.L. and A.L.-R. performed the statistical analyses. E.R., S.L., and L.P. and A.L-R. performed the study visits. E.R., S.L., J.O., P.N. and A.L.-R. participated in study planning. R.A. performed [^{18}F]FTHA radiotracer metabolite analysis. E.L. drafted the first version of the manuscript, and all authors reviewed the text and approved of the final version. A.L.-R. is the 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.

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