The following abstract describes the secondary endpoint of intracellular signaling and insulin sensitivity/secretion after Jardiance compared to placebo. The article is expected to be published within few months.

The secondary endpoints of body composition and energy expenditure is published in the attached article together with all primary endpoints. The secondary endpoint of arterial stiffness was unfortunately cancelled due to failed measurements by the Arteriograph24 device.

The primary endpoint of the effect of Jardiance on the kidneys is going to be analyzed in the coming months.

Context. SGLT2 inhibition leads to numerous effects that may contribute to cardiovascular protection during treatment. By excretion of glucose the plasma glucose level drop independently of insulin leading to alterations in adipose tissue metabolism.

Objective. To elucidate the effects of SGLT2 inhibition on the balance between storage and release of fatty acids in adipose tissue.

Design. Randomized, double-blind, placebo-controlled crossover design

Setting. Ambulatory care

Patients. 13 patients with type 2 diabetes>1 years were recruited through advertisements in local press. Patients were treated with metformin, aged 50-70 years and HbA1c was between 48-75 mmol/mol. 12 patients completed the study. 1 patient withdrew because of claustrophobia during scans.

Intervention. Four weeks of empagliflozin 25 mg and placebo once-daily

Main Outcome Measures. Lipid storage and lipolysis in adipose tissue analyzed with an LPL-activity assay, western blotting and qPCR for protein and mRNA abundance, respectively. An

oral glucose tolerance test was performed to study adipose tissue insulin resistance. Finally, PET/CT examinations were studies to estimate adipose tissue glucose and palmitate uptake together with whole body FFA clearance and lipolysis rate.

Results. Four weeks of SGLT2 inhibition lead to a 26% reduction in both GLUT4 protein level (p=0.03) and mRNA level (p=0.01). Furthermore, we found G0S2 mRNA expression to decrease by 15% (p=0.01) and FFA uptake in visceral adipose tissue to increase by 27% (p<0.05). Adipose tissue insulin resistance and insulin signaling remained unaffected by the intervention.

Conclusions. SGLT2 inhibition affect lipid storage in adipose tissue through reductions in GLUT4 gene and protein expression which probably reflects a reduced glucose oxidation and lipid storage. Furthermore, treatment with SGLT2 inhibition decrease G0S2 mRNA and hence increase lipolysis. Adipose tissue insulin sensitivity remained unaffected by the intervention.

Commented [KML1]: Jeg er igen i tvivl om, hvorvidt visc fedt FFA optaget skal fremhæves, så længe vi ikke kan sætte det i større perspektiv med literaturen.