The efficacy of SGLT2 inhibitors to delay the onset of diabetes mellitus

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INTRODUCTION

- Diabetes mellitus type 2 (DMT2) is a worldwide spreading pandemic.
- Prevention is the best medicine.
- The sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a new family of anti-diabetes drugs.
- Function at the kidney to inhibit glucose re-absorption.
- Recombinant congenic mice strain models of human obesity-induced DMT2 and metabolic syndrome may help us test the preventive efficacy of the SGLT2i.

HYPOTHESIS AND AIMS

We hypothesize that early SGLT2i treatment will delay the onset of DMT2. The main aim is to evaluate efficacy of SGLT2i on the latency to develop full scale DMT2. Additionally, we are assessing secondary parameters such as kidney function, glucagon and glycogen levels and mice behavioral changes.

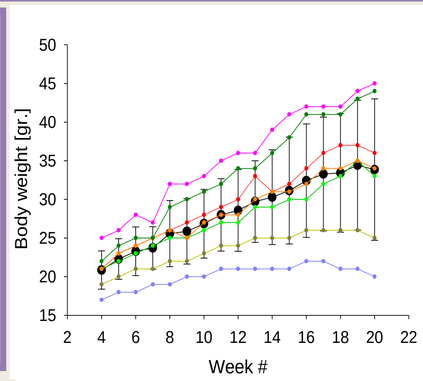
METHODS

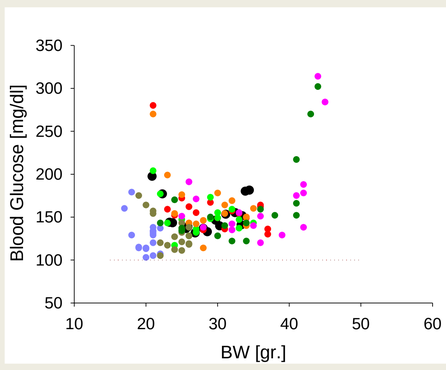
Three week old male mice were divided into 2 experimental groups. A. untreated mice, served as control group; B. Empagliflozin 10 mg/kg/day (in the future). Therapy will be administered from the third week till the 20-th week.

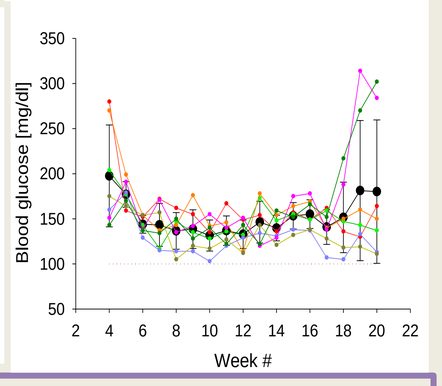
- Mice were monitored weekly for body weight and blood sugar level.
- All mice were undergoing basal motoric and sensory tests.
- Mice underwent 24 hours urine collection for its volume, electrolytes composition, protein concentration and creatinine level in metabolic cages.
- Measurements were repeated at 4 weeks and before sacrifice,12 weeks of experiment.
- Upon last physiological assessment, mice were euthanized, blood was collected, and specific organs were harvested (Liver, kidney, pancreas and heart).
- Harvested organs were divided and preserved for histology (in 4% paraformaldehyde) and for molecular biology (by flash freezing in liquid nitrogen).

RESULTS

- Body weight (BW) and Blood glucose level as a function of time, and as a function of each other. Dotted red line - hyperglycemia threshold (100 mg/dl), (•) represent mean data, colored symbols - individual mice.
- NonC mice did not developed considerable diabtetes.

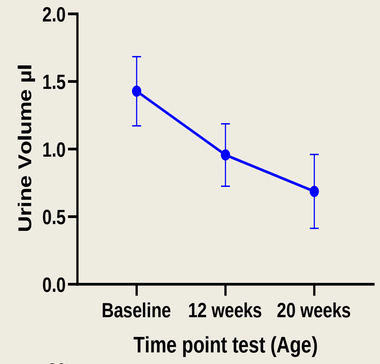


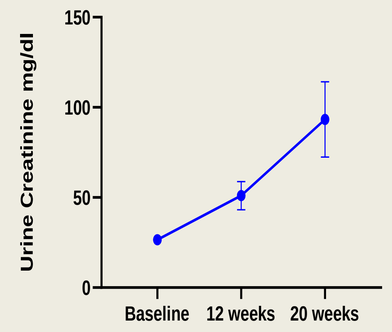


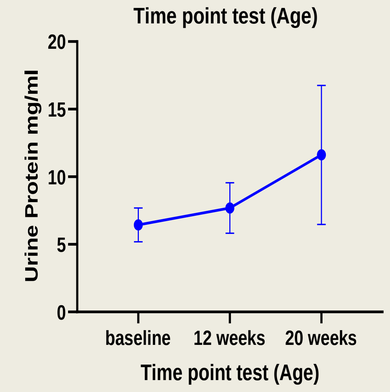


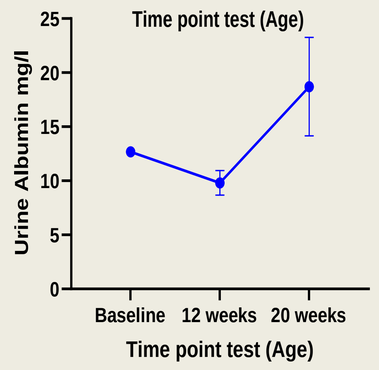
Metabolic data

Urine analysis indicate the development of concomitant renal dysfunction.

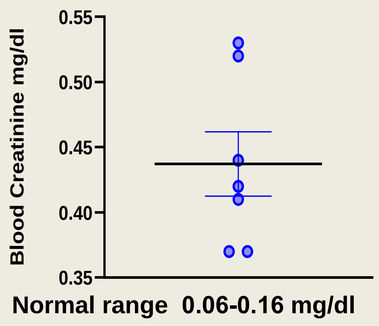


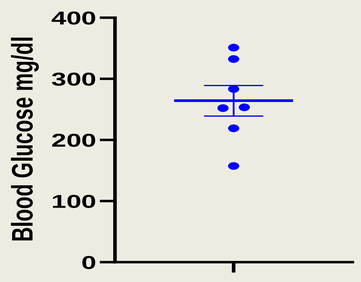




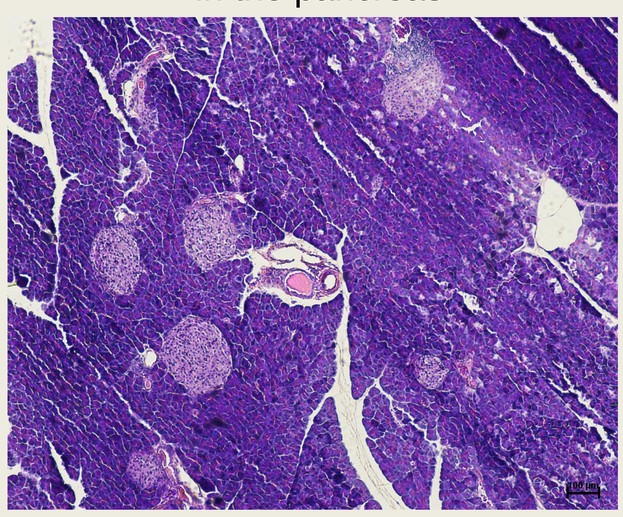


Blood analysis at final time point (age 20 weeks)
Mean+SD and individual results

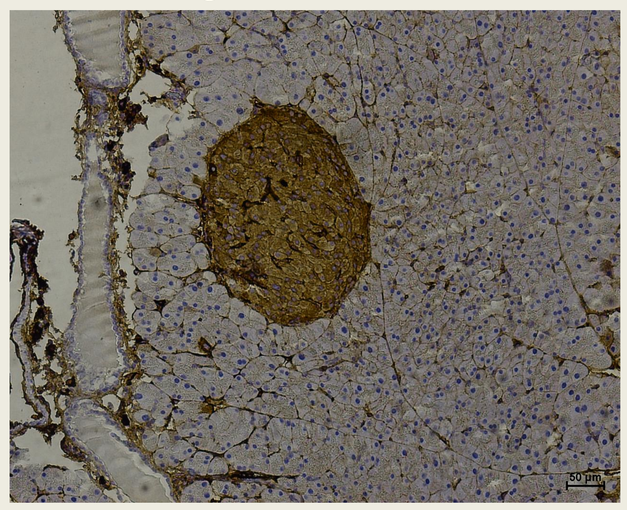




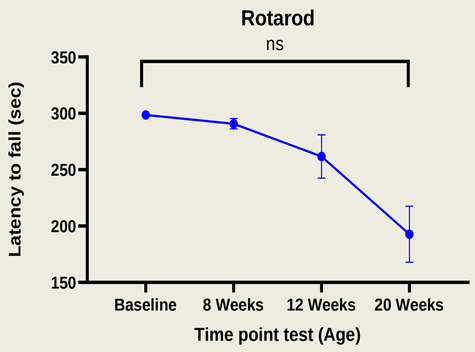
Density of the Langerhans Islands in the pancreas



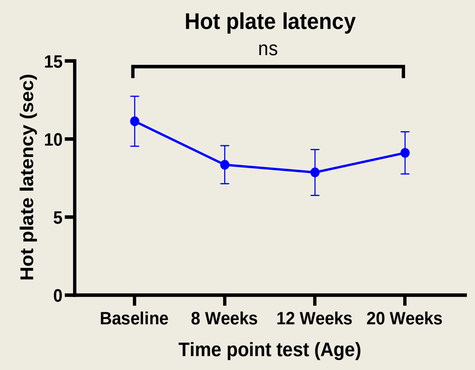
Insulin staining in the Langerhans Islands

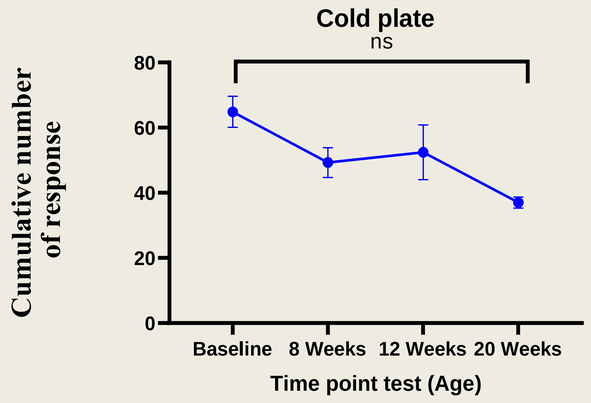


	Mean±SD	Median
Insulin % of islets	70.3±10.4	69.4
islets area (um)	39319.4±33441.3	20616.5
islets area % of tissue	2.401±1.834	1.312



Motor and sensory parameters: Diabetes attenuates some motoric and sensory responses





CONCLUSIONS

- NonC mice due to develop severe diabetes (glucose <300 mg/dl) within 8 weeks.
- The preliminary results show that the NonC mice did not develop significant diabetes as expected.
- We are considering replacing mice strain (db/db), which due to develop severe diabetes (glucose >300 mg/dl) within 5 weeks.

CLINICAL IMPLICATIONS

The study might add new indications to SGLT2i. i.e. as a preventive treatment, that will enable diabetes onset delay, or prevented altogether.