

Soluble Epoxide Hydrolase Inhibitors May Delay Diabetes Onset in the UC Davis Type 2 Diabetes Mellitus Rat Model

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is a serious and increasingly prevalent metabolic disease that is characterized by increased blood glucose levels, insulin insensitivity, and β -cell/islet dysfunction. One of the central components of the pathophysiology of T2DM in humans is a general inflammatory state which can be prophylactically or therapeutically targeted. One potential way of targeting this dysregulation is via soluble epoxide hydrolase inhibitors (sEHI) which have been shown to have anti-inflammatory effects. We investigated the therapeutic properties of a novel sEHI in the UC Davis Type 2 Diabetes Mellitus rat model. During this pilot study we performed a dual treatment of fish oil and the sEHI on the UC Davis T2DM Rat Model, targeting the inflammatory etiology. The treatment and control groups were n=6. The goal of the study is to see if sEHIs have a protective effect by delaying T2DM development in the UC Davis T2DM rat model. We assessed this by measuring: non-fasted glucose, fasted glucose, HbA1c, serum triglyceride, total cholesterol, oral glucose tolerance tests, food intake, and water intake. Comparisons between groups were done with 2-way ANOVAs. From our preliminary results we observed some positive effects from the fish oil and sEHI on the treatment group as demonstrated by: delayed diabetes onset; lower blood glucose, triglyceride, and total cholesterol levels; and improved glucose tolerance during an oral glucose tolerance test (OGTT). These preliminary results suggest sEHIs and fish oil in combination have a prophylactic effect by delaying onset of T2DM and that further investigation of these effects and underlying mechanisms is warranted.

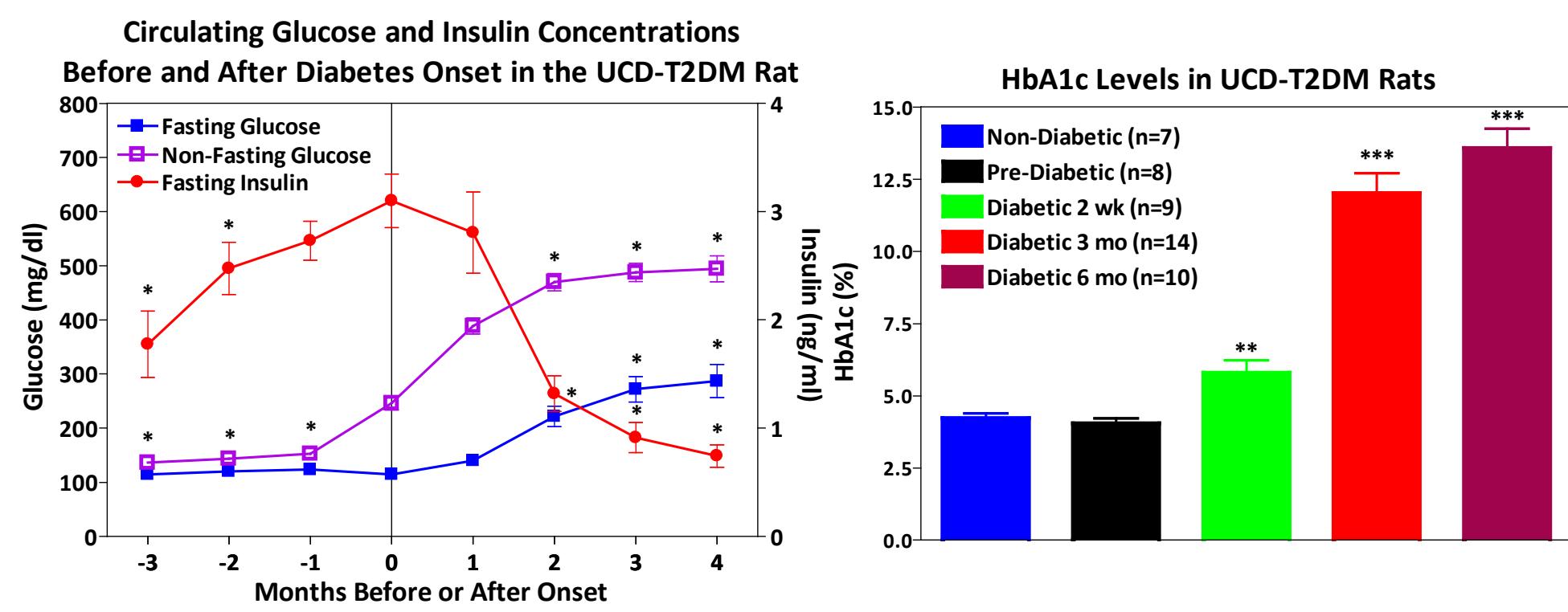
INTRODUCTION

- A key factor in the pathophysiology underlying the development of T2DM in humans is low-grade systemic inflammation (Duncan et. Al. 2003)
- sEHIs target the cytochrome p450 pathway of the arachidonic acid cascade and are anti-inflammatory (Morisseau and Hammock, 2013)
- Fish oil has also been demonstrated to have anti-inflammatory properties (Bremer et. Al., 2013)
- Our hypothesis is that the combined sEHI and fish oil treatment will delay the onset of T2DM

METHODS

UC DAVIS TYPE 2 DIABETES MELLITUS RAT MODEL

- This model of T2DM better replicates human diabetes due to its intact leptin signaling and polygenic diabetic origin
- Was created by crossing lean Zucker Diabetic Fatty and obese Sprague-Dawley rats
- Development and progression of T2DM in this model is dependent on both peripheral insulin resistance and insufficient beta cell compensation, like in humans (Cummings et. Al., 2008)

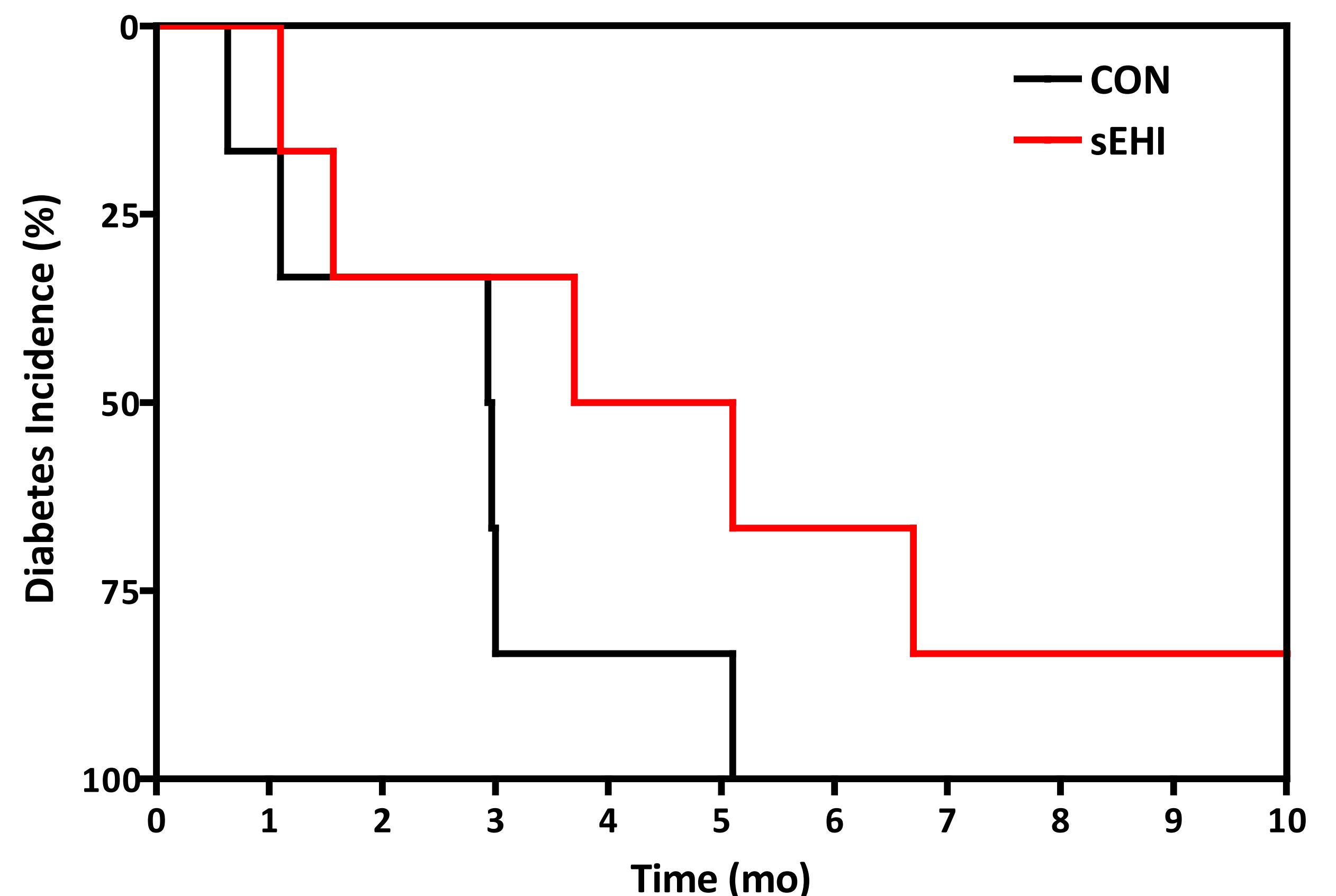


STUDY DESIGN

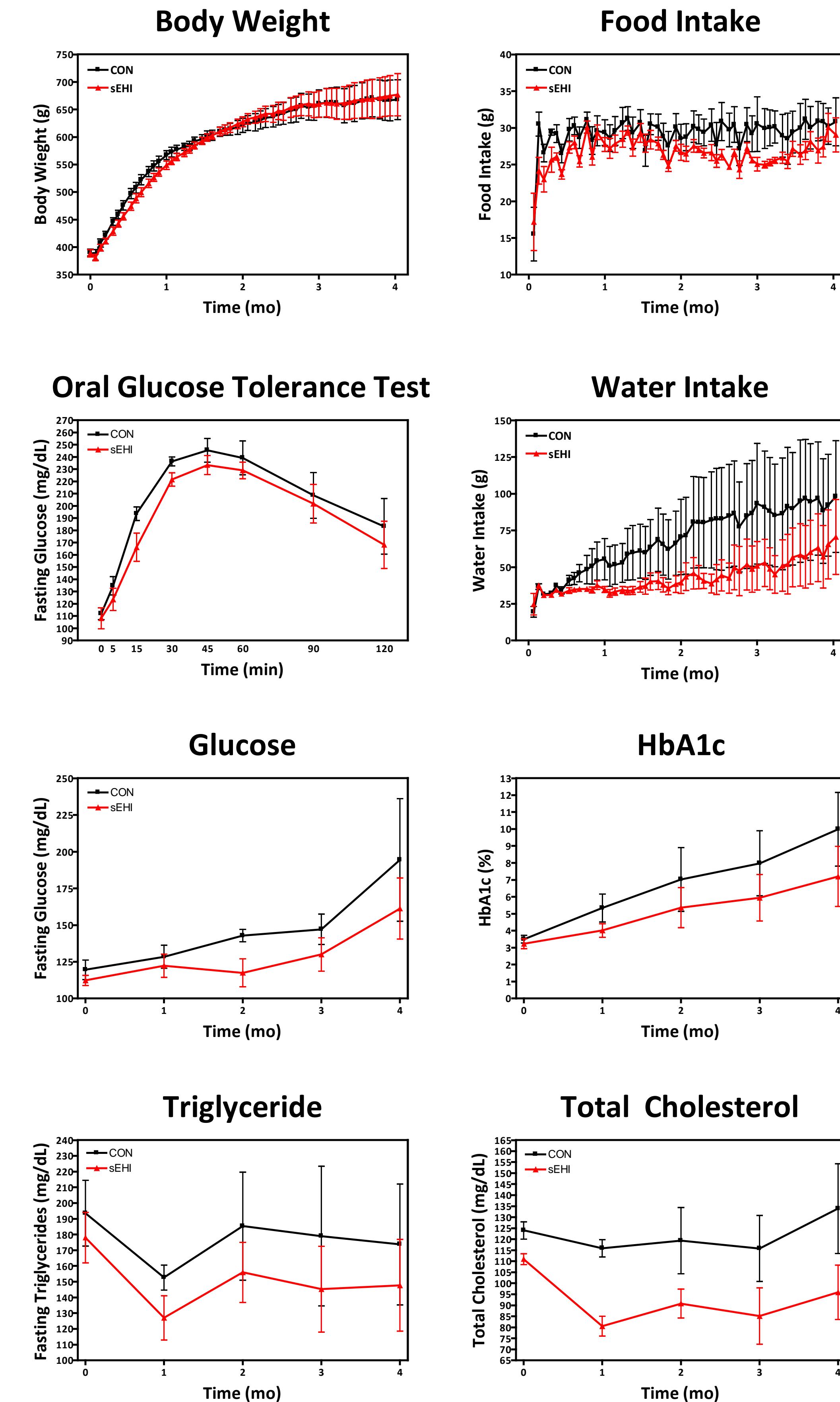
- Two groups of the UCD T2DM rat model, treatment and control groups (n=6) were studied.
- Animals enrolled in study at 2 months of age
- Both groups received 6% oil by weight in their chow diet. Animals in the treatment group received fish oil (5% EPA and 25% DHA). Control animals received a control oil (Wesson Best Blend®)
- Treatment group also received the TPPU (sEHI). TPPU was given at 5mg/mL in 1% PEG400 drinking water. Control animals were given 1% PEG400 drinking water
- Fasting blood samples were collected every month until 6 months of age
- Diabetes incidence, food intake, water intake, glucose (Fisher Scientific), triglyceride (Sigma), total cholesterol (Fisher Scientific), were monitored for 10 months and oral glucose tolerance tests were performed
- Diabetes onset was defined as 2 sequential, weekly non-fasted blood glucose readings >250mg/dL
- 2-way ANOVAs of percent change data were performed for glucose, triglyceride, and total cholesterol
- Logrank test was used for diabetes incidence comparison

RESULTS

Diabetes Incidence



- Diabetes onset is delayed in the group treated with fish oil and sEHI but not significantly
- Blood glucose, HbA1c, total cholesterol, and triglyceride levels are reduced in the fish oil and sEHI group but not significantly
- Area under the curve (AUC) for the fish oil and sEHI treatment group was reduced for the oral glucose tolerance tests but not significantly



CONCLUSIONS

- These results from the interim analysis of our ongoing study suggest that the fish oil and sEHI treatment in combination have the potential to delay diabetes onset and produce improvements of diabetes-related metabolic parameters in UCD-T2DM Rats.
- The initial data are promising and warrant further expansion of this pilot study to a more comprehensive study that includes a substantially larger number of animals to determine statistical significance and examine additional metabolic and inflammatory outcomes.