Plan Overview

A Data Management Plan created using DMPTool

Title: Targeting Hepatic Mitochondrial Oxidation to Treat NAFLD, NASH and T2D

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Affiliation: Yale University (yale.edu)

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Project abstract:

Type 2 diabetes (T2D) and nonalcoholic fatty liver disease (NAFLD) are emerging as two of the most critical global health challenges of the 21st century. NAFLD is estimated to affect up to one third of the general population, and NAFLD is nearly universally present in patients with T2D, with 75-100% of participants demonstrating hepatic steatosis, and with 50% and 19% demonstrating nonalcoholic steatohepatitis (NASH) and cirrhosis, respectively. Furthermore, NAFLD represents the most common cause of liver disease in children and adolescents. Studies by our group and others have shown a strong relationship between NAFLD, hepatic insulin resistance and T2D, however the cellular mechanisms that lead to hepatic insulin resistance and increased gluconeogenesis remain to be established. The studies proposed in this grant build on our previous studies that have shown that reduction of hepatic fat content through enhancement of hepatic mitochondrial lipid oxidation can reverse hepatic insulin resistance and diabetes in rodent and nonhuman primate models of NAFLD, NASH and T2D. The **Overarching Aims** that will be addressed in this grant will be to determine if rates of hepatic mitochondrial oxidation are altered in NAFLD, NASH and T2D and whether promoting chronic increases in rates of hepatic mitochondrial fat oxidation by means of a chronic glucagon infusion delivered by minipump will reduce hepatic steatosis and hepatic insulin resistance in individuals with NAFLD. To address these questions we will apply a novel **P**ositional **I**sotopomer **N**MR **T**racer **A**nalysis (**PINTA)** method that we have recently developed to: i) Assess rates of hepatic mitochondrial oxidation, pyruvate carboxylase flux and hepatic ketogenesis in participants with NAFLD, NASH and type 2 diabetes, ii) Assess the acute effects of a physiological increase in plasma glucagon concentrations, both in the presence and absence of compensatory hyperinsulinemia, on rates of hepatic mitochondrial oxidation, hepatic pyruvate carboxylase flux and hepatic ketogenesis in control and NAFLD participants and iii) Assess the effects of chronic glucagon treatment on rates of hepatic mitochondrial oxidation, pyruvate carboxylase flux, hepatic ketogenesis, hepatic fat content and hepatic insulin sensitivity in individuals with NAFLD. Taken together the results of these studies will provide

important new insights regarding the role of altered hepatic mitochondrial function in the pathogenesis of NAFLD, NASH and T2D, which in turn will have important implications for the development of novel liver-targeted mitochondrial uncoupling therapies aimed at increasing hepatic mitochondrial fat oxidation to treat NAFLD, NASH and T2D, which are currently being evaluated in Phase 2b trials. The present study will also provide critical information regarding the acute and chronic effects of glucagon on hepatic mitochondrial oxidation, hepatic gluconeogenesis, hepatic insulin sensitivity and hepatic fat metabolism which has important implications for dual GLP-1/glucagon agonists and triple GLP-1/GIP/glucagon agonists which are now being evaluated in clinical trials for treatment of obesity, NAFLD, NASH and T2D.

Start date: 12-01-2023

End date: 11-30-2028

Last modified: 02-15-2023

Copyright information:

Targeting Hepatic Mitochondrial Oxidation to Treat NAFLD, NASH and T2D

We will generate semi-targeted metabolomics and metabolic flux data, as well as physiological outcomes related to liver mitochondrial metabolism via the following methods: GC-MS, LC-MS/MS and NMR, COBAS, 1H MRS. We expect to generate the the following data file types and formats during this project: .xlsx and .pzfx files.

Appropriate measures will be used for data de-identification and sharing, and informed consent forms will reflect those plans. In this proposed project, the cleaned, item-level spreadsheet data for all variables will be shared openly, along with example quantifications and transformations from initial raw data. Final files used to generate specific analyses to answer the Specific Aims and related results will also be shared. The rationale for sharing only cleaned data is to foster ease of data reuse.

Documentation and support materials will be compatible with the clinicaltrials.gov Protocol Registration Data Elements.

The data obtained from this study will not require the use of specialized tools to be accessed or manipulated.

Data will be stored in common and open formats, such as .xlsx and .pzfx files. Information needed to make use of this data along with references to the sources of those standardized names and metadata items will be included wherever applicable.

Aggregate clinical trial data generated from this study will be available in clinicaltrials.gov. All other data will be archived through the Common Fund-supported Open Science Framework.

The Open Science Framework provides metadata, persistent identifiers (unique URL), and long-term access. This repository is supported by the Common Fund and dataset(s) are available free of charge to any user.

Shared data generated from this project will be made available as soon as possible, and no later than the time of publication or the end of the funding period, whichever comes first. The duration of preservation and sharing of the data will be a minimum of five years after the end of the funding period.

There are no anticipated factors or limitations that will affect the access, distribution or reuse of the scientific data generated by the proposal.

Controlled access will not be used. The data that is shared will be shared by unrestricted download.

In order to ensure participant consent for data sharing, IRB paperwork and informed consent documents will include language describing plans for data management and sharing of data, describing the motivation for sharing, and explaining that personal identifying information will be removed.

To protect participant privacy and confidentiality, all shared data will be de-identified by removing the association between a set of identifying data and the data subject following HIPAA guidelines.

Dr. Gerald Shulman (ORCID ID: 0000-0003-1529-5668) and Dr. Kitt Petersen (ORCID ID: 0000-0003-2664-670X) will be responsible for the day-to-day oversight of lab/team data management activities and data sharing. Broader issues of DMS Plan compliance oversight and reporting will be handled by the Co-PIs and Co-I team as part of general Yale School of Medicine stewardship, reporting, and compliance processes.