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Title of project: Cardiac and hepatic metabolic flexibility in fatty liver disease: Impact of NAFL and NSH in type 2 diabetes and of GLP-1 recept

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) has recently been shown to predict heart failure as well as early oxidative abnormalities in the heart. Unfortunately, the incidence of NAFLD is rapidly growing as a result of the increased burden of obesity and type 2 diabetes. Whether the metabolic abnormalities are specific to the heart or uniformly associated with metabolic changes in the liver and peripheral tissues (skeletal and adipose tissue) is presently unknown and no information exist on the different stages of NAFLD, i.e. simple steatosis (NAFL) and the more severe version, steatohepatitis (NASH). Strategies to reverse NAFLD are scarce, but treatment with GLP-1 receptor agonist has been suggested to be useful, although at present no specific treatment recommendation
exists.
In the proposed studies, we will, for the first time, use 11C palmitate PET, 11C acetate PET, 18FDG glucose PET tracers, in combination with VLDL-TG and palmitate tracers, echo-cardiography and tissue biopsies to determine the direct relationships between cardiac, hepatic, skeletal muscle and adipose tissue substrate handling (FA, glucose and VLDL-TG kinetics and oxidation) to confirm or refute the hypothesis that coordinated cardiac, hepatic, skeletal and adipose tissue metabolic abnormalities exist with respect to fuel (FA and glucose) metabolism and cardiac contractility in type 2 diabetic subjects with NAFLD and NASH and that these abnormalities are modified by treatment with a GLP-1 agonist (semaglutide).

ABSTRAKT

Det er for nyligt blevet beskrevet, at nonalkoholisk fedtleversygdom (NAFLD) kan forudsige hjertesvigt og tidlige oxidative abnormaliteter i hjertet. Uheldigvis er forekomsten af NAFLD hurtigt voksende på grund af det stigende antal patienter med fedme og type 2 diabetes. Hvorvidt de metaboliske abnormaliteter er begrænset til hjertet eller om de er mere bredt associeret med metaboliske abnormaliteter i leveren og i det perifere væv (skelet muskulatur og fedtvæv) vides ikke, og der er ingen information omkring de forskellige stadier af NAFLD som den simple steatose (NAFL) eller den mere alvorlige version, steatohepatitis (NASH).
Mulighederne for at behandle NAFLD er begrænsede, men det er blevet foreslået at glucagon lignende peptid 1 (GLP-1) receptor agonister er gavnlige, selvom der på nuværende tidspunkt ikke findes en behandlingsindikation. I dette projekt, vil vi benytte forskellige metoder som C^{11} palmitat positronemissionstomografi (PET), C^{11} acetate PET, og F^{18} fluorodeoxy-glucose PET sporstoffer i kombination med det fedttransporterende partikulære stof VLDL-TG sporstoffer, ekkokardiografi

samt vævs-biopsier til at bestemme den direkte forbindelse mellem hjerte, lever, skelet muskulatur, og fedtvæv substrat omsætning (fedtsyre, glukose og VLDL-TG kinetik og oxidation) til at bekræfte eller afslå følgende hypotese: At der eksisterer fælles metaboliske abnormaliteter i hjertet, leveren, skelet muskulaturen samt fedtvæv i forhold til omsætningen af metabolitter (fedtsyre og glukose) og sammentrækningsevnen af hjertet hos type-2 diabetes individer med NAFLD og NASH, og at disse abnormaliteter kan modificeres med GLP-1 agonist behandling (semaglutide).