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Title of project: The impact of non-alcoholic fatty liver disease on hepatic glucagon sensitivity and amino acid turnover

ABSTRACT

Type 2 diabetes and the metabolic syndrome are associated with non-alcoholic fatty liver disease (NAFLD), which has become the most common liver disease with an estimated global prevalence of 25% (1). The increase in NAFLD parallels the global rise in obesity, and the pathophysiology is closely linked to chronically high caloric intake promoting continuous deposition of fat in hepatocytes (2). Obesity-related insulin resistance and ensuing hyperinsulinaemia exacerbates the deposition of lipids in the liver and, thus, contributes to NAFLD development (3). Increasing evidence supports the existence of a feedback cycle between hepatic amino acid metabolism and the secretion of glucagon from pancreatic alpha cells. The development of NAFLD is thought to disrupt this relationship and promote hyperglucagonaemia, which in turn contributes to the hyperglycaemia of patients with type 2 diabetes (4,5). However, this has only been tested in a cross-sectional setting in humans. A carbohydrate-based high caloric diet induces NAFLD within weeks, and the studies forming the basis of the present application will examine the impact of NAFLD induction on hepatic amino acid metabolism in response to glucagon infusion, i.e. hepatic glucagon sensitivity. The degree of steatosis will be evaluated by magnetic resonance spectroscopy. This will provide important mechanistic insight into the liver-alpha cell axis and potentially delineate new targets for the treatment of NAFLD and type 2 diabetes.