Henning och Johan Throne-Holsts stiftelse för främjande av vetenskaplig forskning

Report after my stay as a postdoctoral research fellow at the University of Oxford, Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM), Oxford, United Kingdom (February – April 2015).

I would like to start to express my deepest gratitude for giving me the opportunity to finalize the studies I was working on during my previous time (October 2012 – September 2013) at the University of Oxford. In one of these studies, we investigated gender-related differences in postprandial hepatic lipid metabolism. Eleven women and eleven men, with similar age, BMI and liver fat content consumed a mixed meal labelled with stable-isotopes (^2H_2O and [$U^{13}C$]palmitate) to trace the fate of newly synthesized and dietary lipids. We found men to have higher fasting and postprandial plasma triacylglycerol concentrations, lower dietary fatty acid oxidation, and greater hepatic *de novo* lipogenesis compared to women. This represent partitioning of fatty acids into esterification and storage pathways within the liver leading to greater very low density lipoprotein triacylglycerol (VLDL-TG) production and may explain the observed sexual dimorphism in prevalence and risk of hepatic steatosis. We have now finalized this manuscript and it is under review in the Journal of Hepatology.

In the other study, we aimed to understand the metabolic consequences of *de novo* lipogenesis (DNL), which has been implicated in the pathogenesis of insulin resistance and hepatic steatosis, in individuals across a spectrum of liver fat (metabolically "healthy" and "unhealthy" overweight individuals). We investigated differences in postprandial hepatic fatty acid partitioning (using stable-isotope methodologies) in men and women with varying degrees of hepatic DNL, divided by median hepatic DNL. We found no difference in liver fat content between the low (n=20) and high (n=21) DNL groups but subjects with high compared to low DNL were more insulin resistant and had a greater amount of android fat. Over the course of the postprandial period the high DNL group had a significantly greater incorporation of labelled dietary fatty acids into VLDL-TG and lower dietary fatty acid oxidation. Thus, enhanced hepatic DNL is associated with insulin resistance and influences hepatic fatty acid partitioning by de-routing dietary fatty acids into esterification rather than oxidation pathways which may ultimately lead to liver fat accumulation. This manuscript has just been finalized and sent to co-authors for comment and will be submitted within the coming weeks.

During my studies in Oxford, I was also involved in a study in which we determined the stability of the ketone body acetoacetate in different blood fractions (plasma, whole blood and red blood cells). We also assessed the postprandial response of acetoacetate in different blood fractions to determine possible differences between these fractions during the postprandial phase. This study has been published and is attached with this report. Moreover, we wrote a

review article about experimental models and their usefulness to understand the aetiology and development of non-alcoholic fatty liver disease. This review has also been published and is attached with this report.

Future projects

I am involved in a study aiming to investigate how supplementation with fish oil [n-3 fatty acids (EPA and DHA)] affects postprandial fatty acid partitioning – specifically how these fatty acids decrease plasma triacylglycerol concentrations, their influence on hepatic lipid accumulation and cholesterol metabolism. All subjects have been enrolled and analyses are currently ongoing.

I had the opportunity to use data from the Oxford Biobank (www.oxfordbiobank.org.uk) to search for single nucleotide polymorphisms (SNPs) in a specific gene of interests associated with plasma lipoprotein and apolipoprotein concentrations. A SNP in this gene was found to be associated with lower apolipoprotein B concentrations in women and a collaboration to further investigate this SNP has been initiated.

Budget

I followed the budget which made it possible for me to afford double costs of living.

Again, thank you for giving me this great opportunity which will be of great value for my future research projects.

Best wishes,

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