

Tissue-specific insulin resistance in human obesity

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Summary

Over the last decades, the prevalence of obesity has reached epidemic proportions and obesity and its metabolic consequences are major contributors to morbidity and mortality worldwide. Obesity is strongly linked to the development of insulin resistance, which in turn is a major risk factor in the development of cardiometabolic diseases. Insulin resistance can develop simultaneously in multiple organs and severity may vary between organs. Over the years, it has been convincingly shown that there is a complex interplay between metabolic insulin sensitive organs involved in lipid metabolism, such as adipose tissue, skeletal muscle and liver. In addition, impairments in lipid metabolism play an important role in the development and progression of insulin resistance. The present thesis therefore aimed to study multiple aspects of lipid metabolism in relation to whole-body and tissue-specific insulin resistance using a physiological approach.

In **chapter 2** we studied the contribution of endogenous and dietary fatty acid sources to skeletal muscle uptake and storage in overweight or obese individuals with a wide range of insulin resistance. To study the metabolic fate of dietary versus endogenous fatty acids, a dual stable isotope technique was applied. [^{13}C]-palmitate was added to a high-saturated fatty acid mixed meal to label chylomicron-triacylglycerol (TAG) (i.e. exogenous or dietary TAG) in the circulation. Simultaneously, [$^2\text{H}_2$]-palmitate was infused intravenously to label endogenous fatty acids. As [$^2\text{H}_2$]-palmitate can be incorporated into newly synthesized TAG in the liver, [$^2\text{H}_2$]-labelled TAG reflects very-low-density-lipoprotein (VLDL)-TAG (i.e. endogenous TAG) in the circulation. This stable isotope technique was combined with measurements of arterio-venous concentration differences across the forearm muscle to investigate skeletal muscle fatty acid handling and the specific contribution of the different fat sources to skeletal muscle fatty acid handling. We showed that insulin resistance is associated with increased postprandial VLDL-TAG extraction across the forearm muscle, despite a similar supply of TAG. In addition, distinct patterns of lipid composition were observed in the skeletal muscle lipid pools in insulin resistance, as reflected by an increased saturation of the intramyocellular non-esterified fatty acid pool. Ultimately, the elevated TAG extraction and an altered intramuscular lipid composition may lead to skeletal muscle insulin resistance, but exact underlying mechanisms remain to be defined.

In **chapter 3** and **4**, we investigated the role of plasma angiopoietin-like protein 4 (ANGPTL4) in skeletal muscle and in abdominal subcutaneous adipose tissue lipoprotein lipase (LPL) activity as reflected by *in vivo* TAG extraction across these tissues.

Chylomicron- and VLDL-TAG are hydrolyzed by LPL in the process of intravascular lipolysis and subsequently fatty acids are extracted by underlying tissues. Insulin is an important regulator of LPL activity, but a considerable part of the variation in LPL activity may also be explained by other factors. The LPL inhibitor ANGPTL4 is an interesting candidate and might be involved skeletal muscle and adipose tissue TAG extraction. In **chapter 3** and **4** we show that plasma ANGPTL4 concentrations were not associated with TAG extraction (e.g. a measure for *in vivo* LPL activity) across the forearm skeletal muscle and abdominal subcutaneous adipose tissue. Interestingly, the data we additionally present in **chapter 4**, indicated that plasma ANGPTL4 might play a role in adipose tissue intracellular lipolysis after weight loss and therefore possibly in lipid partitioning after weight loss. Finally, we provided for the first time *in vivo* evidence that ANGPTL4 is secreted from the human skeletal muscle and adipose tissue after a high-saturated fatty acid mixed meal (**chapter 3** and **4**).

In **chapter 5** and **6**, we acquired more information on distinct insulin resistant phenotypes, which is necessary to develop intervention strategies targeting different tissue-related or prediabetic phenotypes. Tissue-specific insulin resistance was estimated by using a 2 hours oral glucose tolerance test, with glucose and insulin measurements at five time-points. We included cross-sectional data from the Diet, Obesity and Genes (DiOGenes) project, which is a large, multicenter, randomized, controlled dietary intervention study and involved eight European countries. In **chapter 6**, we additionally included individuals from the Cohort on Diabetes and Atherosclerosis Maastricht (CODAM). Both cohorts comprised overweight and obese non-diabetic individuals who are at risk for developing cardiometabolic diseases.

In **chapter 5**, we investigated cross-sectional associations of tissue-specific insulin resistance with the plasma lipidome. 140 plasma lipids were quantified by liquid chromatography–mass spectrometry. We showed a positive association between muscle insulin sensitivity and plasma lysophosphatidylcholine levels in both sexes. Furthermore, we identified sex differences in the associations between hepatic insulin resistance and the plasma lipidome. Hepatic insulin resistance was higher in men compared to women. However, in women an increase of hepatic insulin resistance was associated with an increase in plasma TAG and diacylglycerol and a decrease in the relative abundance of odd-chain and very-long-chain TAG. In contrast, the degree of hepatic insulin resistance did not relate to alterations in the plasma lipidome in men. Combined with the observation that overweight/obese women had less hepatic insulin resistance and lower TAG levels than men, this would suggest that

the plasma lipidome may be more responsive to worsening of hepatic insulin resistance in women, or vice versa.

In **chapter 6** we further characterized tissue-specific insulin resistance phenotypes by studying the abdominal subcutaneous adipose tissue transcriptome by means of RNA sequencing. In individuals with primarily hepatic insulin resistance, extracellular matrix remodeling genes (e.g. collagens) were significantly upregulated, whilst in individuals with primarily muscle insulin resistance, genes related to inflammation (e.g. chemokines and complement activation) were significantly upregulated in abdominal subcutaneous adipose tissue. Subsequent analyses in the CODAM cohort showed that an increased systemic inflammatory profile comprised of eight plasma inflammatory markers may be specifically related to muscle insulin resistance. Based on these findings, we hypothesize that increased abdominal subcutaneous adipose tissue inflammatory gene expression in the muscle insulin resistant phenotype may translate into an increased systemic inflammatory profile, putatively linking subcutaneous adipose tissue inflammation to muscle insulin resistance.

In conclusion, the results from this thesis show distinct metabolic profiles in non-diabetic overweight and obese individuals in relation to (tissue-specific) insulin resistant phenotypes. We showed that insulin resistance is associated with increased postprandial VLDL-TAG extraction across the forearm muscle, despite a similar supply of TAG. As TAG extraction is mediated by LPL in skeletal muscle and adipose tissue, we showed that these results could not be explained by plasma levels of the LPL inhibitor ANGPTL4. In addition, a distinct lipid composition was observed in the skeletal muscle non-esterified fatty acid pool in insulin resistance, which were mainly related to an increased saturation of the intramyocellular non-esterified fatty acid pool. Finally, we showed distinct plasma lipidome and abdominal subcutaneous adipose tissue transcriptome profiles in overweight and obese individuals in relation to tissue-specific insulin resistance phenotypes. These unique metabolic profiles require further mechanistic exploration and may serve as starting point for developing intervention strategies targeting different tissue-related or prediabetic phenotypes.