

# Causes and consequences of lipid overload in skeletal muscle, liver and heart

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## SUMMARY

An obesity epidemic exists worldwide, which in turn is linked to an epidemic of chronic disorders such as type 2 diabetes and cardiovascular disease. Obesity occurs as a result of an imbalance between calories consumed and calories expended resulting in an energy imbalance. This energy imbalance is further caused by overnutrition and physical inactivity. While obesity is characterized by an excessive accumulation of fat in the body, it is specifically the accumulation of fat within peripheral tissues, such as skeletal muscle, liver and heart (steatosis or ectopic fat accumulation) that is associated with the development of insulin resistance, making ectopic fat accumulation a possible link between obesity and chronic metabolic disorders. However, why fat accumulates in ectopic tissues is not completely understood. Increased flux of fatty acids into ectopic tissues has been suggested to lead to disturbances in tissue function, a phenomenon known as lipotoxicity. In this thesis, we investigated the role of plasma free fatty acids (FFA) in lipid accumulation in skeletal muscle, liver and heart.

In chapters 2-5 we manipulated plasma FFA levels physiologically with exercise or pharmacologically with the anti-lipolytic drug Acipimox. We demonstrated that an acute bout of exercise leads to different effects on IMCL depending on whether exercise is performed in a fasted or in a glucose-supplemented condition (chapter 4). In spite of an increased cellular demand of fatty acids during exercise, fat accumulates in skeletal muscle when plasma FFAs are high, whereas when performing exercise in a glucose-supplemented condition IMCL is decreasing in exercising muscle. Likewise, in type 2 diabetic patients, increased plasma FFAs, due to a rebound effect of Acipimox, also led to increased IMCL (chapter 5). This suggests that plasma FFAs are important determinants of IMCL and that skeletal muscle takes up plasma FFA unrestricted when the availability is high, independent of cellular needs.

In contrast to the skeletal muscle, the liver does not accumulate fat as an energy store under conditions of high cellular demand such as exercise training. However, with the current obesity epidemic up to one third of all people with overweight and obesity have elevated lipid content in the liver. In contrast to what is seen with exercise training, one acute bout of exercise was not able to lower hepatic lipid content in men with overweight or NAFLD with the current protocol (chapter 3). Instead, similar to the skeletal muscle, exercise-induced elevations of plasma FFAs

triggered uptake into the liver resulting in increased intrahepatic lipid accumulation four hours post-exercise. Furthermore, we also found a tendency to a lower energy status of the liver four hours post-exercise.

Previous studies have found that also cardiac lipid content correlates with plasma FFA levels, and in line with this, we also found myocardial fat to increase when plasma FFA levels were elevated by means of exercise in this thesis (chapter 2). In type 2 diabetes elevated levels of cardiac lipids have been linked to cardiac dysfunction and lowered cardiac energy status. In support of this, we observed that cardiac energy status, expressed as PCr/ATP ratio, was decreased in parallel with increased cardiac lipid content upon exercise in the fasted state. Surprisingly, however, systolic cardiac function improved rather than decreased upon exercise-induced changes in cardiac lipid content in the same study. This indicates that fat accumulation *per se* is not necessarily detrimental to organ function, at least not on short term. Likewise, in chapter 5, where plasma FFAs were increased due to a rebound-effect of Acipimox-administration, cardiac lipid content and cardiac energy status were unchanged, despite a tendency to decreased cardiac function.

Although plasma FFA levels, as pointed out above, play an important role in ectopic lipid accumulation and the development of insulin resistance, mitochondrial dysfunction is also suggested to be an important determinant of ectopic lipid accumulation. Therefore, in chapter 6, we tried to unravel the relationship between mitochondrial function, ectopic lipid accumulation and insulin resistance. We applied the model of unilateral lower limb suspension, mimicking inactivity in one leg of a subject, while using the other leg of the same individual as an active control. We revealed that inactivity blunts *in vivo* mitochondrial function and reduces fat oxidative capacity while promoting incorporation of fat into intramyocellular triglyceride stores *ex vivo*. Accordingly, intramyocellular lipid content in the inactive leg was higher and blunting of insulin signalling upon lipid infusion more pronounced than in the active leg. Thus, we demonstrated that a physical inactivity-mediated decline in mitochondrial function directly impacts insulin sensitivity under high lipid conditions.

Alpha-hydroxybutyrate has been recognized as a novel biomarker for progressive insulin resistance. In chapter 7 we used samples obtained from a variety of studies in well phenotyped subjects to examine if alpha-hydroxybutyrate could also be a useful marker to detect early changes in insulin sensitivity in future studies. We

demonstrated that indeed alpha-hydroxybutyrate is a marker of insulin resistance. However, alleviation of insulin resistance by exercise training does not necessitate a decline in alpha-hydroxybutyrate and we observed little added value of using alpha-hydroxybutyrate as a predictive marker for insulin resistance relative to conventional markers like fasting insulin and glucose levels.

In conclusion, from the results obtained in this thesis we conclude that plasma FFA concentrations are important determinants of ectopic fat accumulation and that the uptake of FFAs into the ectopic tissue largely depends on FFA availability. By taking up excessive FFA from the circulation, the heart, the liver and the skeletal muscle together act as a buffer contributing to the clearance of FFA from the plasma. Furthermore, excessive cardiac lipid accumulation is not causally related to cardiac function, and changes in plasma FFA and cardiac lipid content do not consistently predict changes in cardiac function. However, increased lipid content in heart and liver were paralleled with a decreased energy status of these tissues; the clinical consequences of this need to be investigated in future studies. For the skeletal muscle, we show that not only elevated plasma FFA, but also decreased physical activity (induced by unilateral lower limb suspension in this thesis), goes along with increased intramyocellular lipid content together with decreased *in vivo* mitochondrial function and oxidative capacity. However, the interrelationship between these parameters is still unknown and should be explored in more detail in the future.