Tissue-specific insulin resistance in human obesity

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Valorization

Knowledge valorization is described by the National Valorization Commission as “the process of creating value from knowledge, by making knowledge suitable and/or available for societal purposes, and suitable for translation into competitive products, services, processes, and new commercial activities”. In this addendum we describe how society may benefit from the work conducted in this thesis.

Our research focused on extending fundamental knowledge about the underlying multiple aspects of lipid metabolism in relation to whole-body and tissue-specific insulin resistance. The main outcomes of the present thesis can serve as starting point for further characterization of different tissue-specific insulin resistant or prediabetic phenotypes. Ultimately, this may provide directions for more targeted and personalized intervention strategies. The valorization potential of these studies will be described in terms of social and economic relevance of obesity research, relevance of measurements for targeted prevention and innovation and translation into practice.

Social and economic relevance of obesity research
The prevalence of obesity has risen to epidemic proportions over the last decades and affects people of all ages and socioeconomic groups (1). More than 39% of the world adult population was overweight (BMI > 25 kg/m²) and about 13% was obese (BMI > 30 kg/m²) in 2014 (2). In 2015, in the Netherlands, over 50% of the individuals over 20 years of age were overweight or obese (3).

The increasing prevalence of obesity is a major health concern. Obesity increases the risk for developing chronic diseases such as type 2 diabetes, cardiovascular diseases, mental disorders, several cancer types and reduces the quality of life. Overweight and obesity are the fifth leading risk for global deaths. 44% of the diabetes burden, 23% of the ischaemic heart disease burden and between 7 – 14% of certain cancers are attributable to overweight and obesity (4). In 2010, overweight and/or obesity was estimated to cause 3.4 million deaths worldwide (5). Additionally, obesity puts an enormous burden on patients, their families, and social health care systems. Therefore, it is important to explore underlying mechanisms that cause obesity and related chronic diseases.

Obesity is linked to the development of insulin resistance, which is a major contributor to hyperglycemia and hyperlipidemia. These are all risk factors towards the development of
type 2 diabetes and cardiovascular diseases. Strikingly, insulin resistance increases the risk for cardiovascular diseases even in the absence of hyperglycemia (6).

From 2011 – 2012, in the USA, the direct cardiovascular disease-related costs were estimated on 193.1 billion US dollars, which reflect e.g. hospital services, prescribed medication and home health care. In addition, indirect cardiovascular disease-related costs, such as loss of future productivity, were estimated to be about 123.5 billion US dollars (7). For diabetes, it has been estimated that the direct annual cost of diabetes to the world is more than 827 billion US dollar (8). Together, for cardiovascular disease and diabetes costs combined, this adds up to more than 1,143 billion US dollars in one year. In 2011, in the Netherlands, the total direct cardiovascular disease-related costs were 8.3 billion euro, which was 9.2% of the total Dutch healthcare costs (89.4 billion euro), while diabetes-related costs were estimated to be 1.7 billion euro (1.9%) (9). Although these numbers cannot only be subscribed to obesity-related cardiometabolic diseases, the expectation is that obesity and thus obesity-related morbidity will continue to increase in the coming years. Therefore, it will have major public health and socioeconomic consequences.

**Relevance of measurements for targeted prevention**

Recognition of symptoms at an early stage and early treatment of obesity and cardiometabolic diseases is important as it may prevent or delay the development of comorbidities. In addition, quality of life will be maintained or improved if weight and blood glucose concentrations can be well-controlled. However, obesity and cardiometabolic diseases are complex metabolic diseases whereby underlying mechanisms are yet not completely understood. Thus, understanding the etiology of obesity and insulin resistance is a key step in the prevention of cardiometabolic diseases. In this thesis, we focused on expanding fundamental knowledge about lipid metabolism in relation to early stages of insulin resistance. Although the findings may not lead to societal benefits at first glance, they generate improved insight into the pathophysiology of lipid metabolism in relation to whole-body and tissue-specific insulin resistance, which adds fuel for thought on future research initiatives.

The various measurements described in this thesis, e.g. plasma lipidomics and adipose tissue transcriptomics, may be future markers to detect the presence of insulin resistance at an early stage. One key finding in this thesis was that distinct plasma lipid profiles were associated with either muscle insulin sensitivity or hepatic insulin resistance in overweight and obese individuals. As an example: we showed that muscle insulin resistance was associated with lower plasma concentrations of the lipid lysophosphatidylcholine. Future clinical and
mechanistic studies will have to investigate whether monitoring lipid profiles as a risk marker will prove to be clinically useful in the treatment or prevention of cardiometabolic diseases.

Importantly, we also observed distinct plasma lipid profiles for men and women. Hepatic insulin resistance was higher in men compared to women. However, in women worse hepatic insulin resistance was associated with an increase in plasma TAG and diacylglycerol concentrations. This aspect of lipid metabolism in relation to sexes is currently very much underemphasized in research and underscores the importance for sex-specific research as this may improve targeted prevention for the individual sexes.

In addition to fasting lipid metabolism measurements, it is a given that the majority of the population in the Western world spends a significant part of the day in the postprandial state. Increasing evidence suggests that not only fasting lipid, lipoprotein and glucose concentrations, but also a disturbed postprandial lipid or glucose metabolism are important risk markers for cardiometabolic diseases. Postprandial measurements are therefore of clinical importance when cardiometabolic disease risk is studied. In chapter 2, we extended existing knowledge on postprandial lipid metabolism. We showed that insulin resistance is associated with increased postprandial very-low-density-lipoprotein (VLDL) triacylglycerol extraction across the forearm muscle, despite a similar supply of triacylglycerol. In addition, different lipid composition patterns were observed in the skeletal muscle lipid pools in insulin resistance, which were mainly related to an increased saturation of the intramyocellular non-esterified fatty acid pool. Ultimately, these events, e.g. elevated skeletal muscle VLDL-triacylglycerol extraction and changes in intramuscular lipid composition, may give rise to increased muscle storage of detrimental bio-active lipid intermediates. They may affect insulin sensitivity in a negative way and contribute to cardiometabolic complications.

**Innovation and translation into practice**

The results described in this thesis have and will become available to the scientific community via publication of scientific reports in international peer-reviewed journals in the field of obesity and diabetes. Additionally, results have been presented at (inter)national conferences to scientists as well as physicians, healthcare professionals and dieticians, working in the fields of obesity, diabetes and metabolism.

Changes in lifestyle are considered to play an important role in the etiology of obesity and cardiometabolic diseases. Manipulation of diet and physical activity are the first-choice treatment for these complications. Lifestyle interventions including combined diet and physical activity have been shown to be effective in the prevention of type 2 diabetes as they
reduce diabetes incidence by 47 - 57% over a 3 - 6 year timeframe (10). In addition to lifestyle interventions, pharmacological modulation may also prevent or delay the onset of cardiometabolic complications (11). Healthcare professionals (e.g. dieticians, physiotherapists and physicians) play an important role in stimulating a healthy lifestyle among individuals who are at increased risk of developing obesity and cardiometabolic diseases. Although the results from this thesis do no provide direct guidelines for healthcare professionals, they provide better insight in metabolic parameters that can be targeted through lifestyle and pharmacological interventions.

In chapter 5 and 6, we showed distinct metabolic profiles for muscle or liver insulin resistant conditions, based on the surrogate insulin sensitivity indexes MIsI and HIRI. We estimated tissue-specific insulin resistance by using a 2 hours oral glucose tolerance test (OGTT), with glucose and insulin measurements at five time-points. Importantly, both indexes were developed and validated against the two-step gold standard hyperinsulinemic-euglycemic clamp in combination with a glucose tracer (12). In the future, these indexes may provide a relatively easy method to classify and identify tissue-specific insulin resistant sub phenotypes as the OGTT is already widely used in the clinic to assess (gestational) diabetes.

In this thesis we revealed distinct metabolic profiles under different tissue-specific insulin resistant conditions, and the exact mechanisms behind this are possibly interesting for the food and pharmaceutical industry to guide development of more personalized targeted nutritional and lifestyle interventions. It should be noted that most associations presented here were based on cross-sectional data and therefore cannot distinguish cause and consequence. But the DiOGenes project is a valuable cohort study for follow-up measurements after diet-induced weight loss and weight regain. Therefore future follow-up of the data after the weight loss intervention may elucidate the temporality of the associations reported or elucidate potential interesting mechanisms. Still, more mechanistic studies are needed to find which pathway(s) need(s) to be targeted to maintain lipid homeostasis and insulin sensitivity.

Notably, key findings of this thesis, i.e. distinct metabolic profiles for muscle or liver insulin resistant conditions, have already served as starting point for developing personalized dietary intervention strategies. Recently, a new research project was started in collaboration with the public-private partnership Top Institute Food and Nutrition (TIFN) to investigate optimal diets to maintain postprandial blood glucose homeostasis in tissue-specific insulin resistant subphenotypes. The ambition of this private-public partnership is to provide the
knowledge base that is needed for more targeted nutritional interventions in the prevention
of cardiometabolic diseases and high-impact innovations in food and nutrition. The close
collaboration between industry and academia leads to demand-driven research with societal
and industrial relevance.

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