Unraveling obesity's road to diabetes and cardiovascular disease

Valorization addendum

Besides education and research, valorization is a main task of universities; the impact of research to society is hereby maximized. Here, the valorization potential of this thesis' main findings will be discussed. We will address the relevance and innovations of this thesis, the framework for future studies on insulin resistance and beta-cell dysfunction, the value of reliability data, and the need for in-depth phenotyping studies.

Relevance of the findings

In order to develop successful strategies to prevent or treat obesity-associated conditions like type 2 diabetes and cardiovascular disease, a thorough understanding of the pathophysiological processes involved is vital. As a substantial proportion of the general population is obese, advances in this area could substantially impact obesity-related morbidity, loss of quality of life, mortality, and health care costs. In this thesis, we identified independent contributors to insulin resistance and beta-cell dysfunction, the two core processes involved in the development of type 2 diabetes. First, we showed that visceral and subcutaneous adipose tissue, intrahepatic lipid and muscle microvascular recruitment are independent contributors to insulin resistance. This means that they constitute separate targets for intervention. Second, we identified NK cells in visceral adipose tissue to induce local and systemic inflammation and thereby contribute to insulin resistance. Third, we identified, in abdominally obese individuals, early alterations in beta-cell function independent from compensatory changes due to insulin resistance, as well as demonstrated that a weight loss intervention can restore these alterations. Fourth, we showed that a part of these obesity-induced changes in beta-cell function could be explained by intrapancreatic lipid. Finally, we demonstrated that a weight loss intervention improved traditional cardiovascular risk factors (e.g., blood pressure, serum cholesterol levels, insulin resistance), as well as some, but not all, vascular function measurements.

Likely, the identification of the independent contributors to insulin resistance and beta-cell function will have a societal impact. The novel findings mentioned above could eventually lead to therapies aimed to intervene with these pathways to prevent, delay the development, or treat type 2 diabetes and cardiovascular disease. Moreover, these findings could lead to the identification of distinct subtypes of obesity, each of which may require a different treatment strategy. Nonetheless, several future studies should be undertaken before these contributors can be considered a true – and safe – therapeutic target. Hence, several ideas for future studies, as well as how their results may impact prevention and treatment strategies will be further discussed below.

Future studies on insulin resistance

Besides the identification of independent tissue contributors to insulin resistance, our novel finding that NK cells in visceral adipose tissue appear to be involved in local and systemic low-grade inflammation and subsequent insulin resistance is particularly valuable. Even though research in rodents demonstrated NK cell accumulation in visceral adipose tissue is an early event into the development of low-grade inflammation and insulin resistance, the cross-sectional design of our studies in humans precludes any conclusions about a temporal association of NK cell accumulation to induction of inflammation and insulin resistance. To provide further evidence for NK cell's involvement in insulin resistance in humans, valuable information can be obtained by studying individuals in whom either NK cells are depleted or who have a loss-of-function mutation. First, those individuals could be evaluated for inflammatory changes in visceral adipose tissue and insulin resistance. Second, an intervention study subjecting NK cell depleted individuals as well as individuals with normal NK cell numbers and function, to short term overfeeding. Ideally, such a study could involve repeated visceral adipose tissue biopsies along with the assessment of insulin resistance. Third, repeated visceral adipose tissue biopsies obtained in intervention studies in obese individuals who are scheduled to undergo repeated abdominal surgery (e.g., bariatric vs. non-bariatric surgery) may provide valuable insights on NK cell's contribution to insulin resistance, as well as the reversibility thereof. Finally, Mendelian randomization techniques may be used to evaluate NK cell involvement in obesity-associated insulin resistance, type 2 diabetes, and cardiovascular disease. Currently, to the best of our knowledge, neither of those study ideas are being investigated. As the data on NK cells in this thesis was the result of a remarkable cooperation between departments, universities and hospitals in this region, the infrastructure to successfully execute studies as those outlined above is already in place.

Future studies on beta-cell function

Whilst the contributors to beta-cell dysfunction are incompletely understood, endothelial dysfunction and lipid accumulation in the pancreas may be involved. To evaluate endothelial dysfunction, the vasodilatory potential of pancreatic arterioles could be determined by means of imaging techniques or ex vivo pressure myography. In humans, pancreatic arterioles are difficult to obtain and the pancreatic vasculature is difficult to assess with current imaging techniques. To probe the concept of pancreatic endothelial dysfunction, studies in animals could be considered to gain arguments for its involvement in beta-cell dysfunction. In addition, the involvement and localization of intrapancreatic lipid can be evaluated by means of electron microscopy images of distinct proportions of human pancreas. Herewith, one can assess whether beta-cells of obese individuals contain intracellular lipid depositions,

as well as identify adipocytes in the direct vicinity of pancreatic (micro)vasculature. As electron microscopy images of relatively large proportions of human pancreas have been collected in another Dutch research project (Nanoscopy project), it should be feasible to demonstrate whether intracellular lipid depositions in beta-cells of obese individuals exist.

The value of reliability

The reliability of many measurements used in research or clinical practice appears to be misused, incompletely considered, or ignored altogether. Nonetheless, by properly assessing and interpreting the reliability of measurements, study designs, power calculations and decision making in clinical practice could benefit substantially. In this thesis, the reliability of a multitude of anthropometric, vascular, metabolic and inflammatory measurements has been assessed. Reliability data, as presented in this thesis, has been combined with information on a measurement's responsiveness to a dietary weight loss intervention. As a result, the study design, power calculation, and selection of measurements has already impacted several studies at our department. Moreover, insight into sources of error have been identified and addressed accordingly. Collectively, this reduces the amount of money wasted on studies with a high probability of a type 2 error (e.g., due to overestimation of a measurement's reliability), as well as the time and money spent on measurements that are unsuited for a certain study design or population.

The potential of in-depth phenotyping in intervention studies

Perhaps above all, this thesis illustrates the potential of combining in-depth phenotyping, accurate and state-of-the art measurements, and multiple mediation analyses. It allowed for the identification of mutually independent contributors to insulin resistance and beta-cell dysfunction. In contrast to the majority of research papers in this field, we probed competing theories within a single study. By performing multiple mediation analysis in a randomized controlled trial, we could probe whether changes in certain variables contributed to changes in an outcome variable. Hence, this provided additional arguments for the involvement of certain pathways. If this approach (i.e., the simultaneous measurement of potential contributing variables to an outcome, ideally with little measurement error) were implemented more often in clinical trials, competing theories could be tested. Such an insight would lead to more targeted therapies, as well as reduce the number of studies needed to be conducted in a field of research.