VALORIZATION
SOCIAL RELEVANCE

The worldwide prevalence of obesity has increased enormously over the last decades and numbers are still increasing every year. According to the World Health Organization, 13% of the world’s adult population (11% of men and 15% of women) was obese in 2014, while in the same year, obesity affected around 18.5% of men and 19% of women in The Netherlands [1]. If post-2000 trends continue, this global prevalence of obesity is suggested to reach 18% in men and 21% in women by 2025. Obesity is associated with an increased risk of developing chronic diseases, including insulin resistance [2], type 2 diabetes [3], cardiovascular diseases [4] and certain types of cancer [5, 6]. To reduce these obesity related comorbidities, nowadays, millions of people are in need of medication, such as glucose-, cholesterol- and/or blood pressure lowering medication, and surgical treatments such as gastric bypass or cardiovascular surgery. Since obesity is a major public health issue and one of the most important risk factors for the development of metabolic diseases, it is clear that the increasing obesity prevalence has major socioeconomic consequences [7]. National and international guidelines recommend changes in modifiable lifestyle characteristics, such as diet and physical activity for both prevention and management of metabolic diseases [8]. While weight loss has been shown to be effective in reducing disease risk, implementation of the recommended lifestyle in the long-term is often hard to maintain by the majority of people. Therefore, to reduce the incidence of obesity and thereby partly improving global health, it is important to obtain better insights in the development and treatment of obesity and related metabolic diseases and to implement new treatment strategies. The results described in this thesis contribute to a better understanding of the role of adipose tissue metabolism in cardiometabolic health and obesity, and provide leads for possible treatment strategies to reduce or prevent obesity and cardiometabolic complications.

TARGET GROUPS

Scientific community

The results described in this thesis have and will become available to the scientific community via publication of scientific articles in international peer-reviewed journals. 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.

Industry

A part of this thesis was accomplished by the close collaboration between academia and industry and research outcomes are of valuable information to the academic community and both the nutritional and the pharmaceutical industry. The industrial partners can translate the research outcomes to develop improved or novel treatment strategies or products that help to prevent or reduce the prevalence of obesity and obesity-related complications. More specific, the nutritional industry can translate the results from chapter 2 in defining new
nutritional targets. The pharmacological industry can use the results from this thesis to develop and/or implement new or improved pharmacological therapies or to expand the rationale for prescribing certain cardiovascular drugs in metabolically compromised conditions, since in our studies combination therapy with sacubitril/valsartan was shown to improve both cardiovascular and metabolic risk factors.

Health care professionals

Healthcare professionals (e.g. dieticians, physiotherapists and physicians) play an important role in stimulating a healthy lifestyle among patients and people at increased risk of developing obesity and related complications. On the other hand, physicians prescribe drugs to reverse for example cardiovascular risk (e.g. hypertension) or to improve glucose metabolism and insulin sensitivity. Although the results from this thesis do not provide direct guidelines for healthcare, they provide better insight in metabolic parameters that can be targeted through certain interventions, applied by physicians and other healthcare professionals. Furthermore, this thesis might provide an indication for more targeted prevention programs in high risk groups of the population (i.e. people with both cardiovascular and metabolic risk factors) and it gives more insight in the mechanism of action of a cardiovascular drug (i.e. sacubitril/valsartan) that also has effects on insulin sensitivity and which therefore may alter the rationale for prescription.

ACTIVITIES AND PRODUCTS

In this thesis, we have put forward fatty acid metabolism-related pathways in several metabolically active organs that can be targeted by dietary interventions, thereby improving whole-body glucose metabolism and insulin sensitivity. The results from the nutritional review can potentially lead to novel functional foods or food supplements (e.g. pre- and probiotics, polyphenols, plant sterols, improved dietary fat quality). However, before these novel products will become available on the market, more scientific research is necessary to confirm mechanisms, safety and health benefits in individuals at increased risk of developing cardiometabolic diseases.

The results from the pharmacological intervention with sacubitril/valsartan, which has recently been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of heart failure [9], showed that the combination therapy has a positive effect on cardiovascular and metabolic risk factors. We showed that treatment with sacubitril/valsartan, as compared to the metabolically neutral calcium antagonist amlodipine, improved peripheral insulin sensitivity in obese hypertensive patients. This knowledge will be immediately used by the pharmaceutical industry. Moreover, sacubitril/valsartan may be a promising alternative for the treatment of hypertension in patients who are at increased risk for developing chronic metabolic diseases (e.g. hypertensive individuals with impaired glucose metabolism).
The exercise training intervention studies showed that exercise training beneficially affects body composition and physical fitness and is effective to improve obesity-related disturbances like whole-body insulin resistance. Although 12 weeks of exercise training induced a slight but significant reduction in fat mass, no significant changes in abdominal subcutaneous adipocyte morphology, adipose tissue function, and abdominal subcutaneous adipose tissue lipolysis were observed in obese subjects, irrespective of their baseline metabolic status. Furthermore, we showed that 12 weeks of exercise training did not improve disturbances in subcutaneous adipose tissue lipolysis in obese insulin resistant individuals. It seems that a more pronounced decrease in adipose tissue mass is needed to induce significant changes in adipose tissue metabolism. Currently, it remains to be established which exercise training duration and modality is most optimal to induce beneficial effects in abdominal subcutaneous adipose tissue.

INNOVATION & IMPLEMENTATION

All results described in this thesis are novel findings and have, partly, been performed at the Department of Human Biology and Movement Sciences of Maastricht University Medical Center+ and in close collaboration with other universities and industrial partners within The Netherlands and Europe, using state-of-the-art methodologies for both \textit{in vivo} and \textit{ex vivo} analyses.

An attractive approach, as described in this thesis, is the application of combination therapy, which simultaneously targets more than one biological pathway or mechanism and therefore may be more effective in reducing disease progression because of additional and/or synergistic effects as compared to monotherapies \cite{10} [11]. With respect to the pharmacological treatment with the combination drug, sacubitril/valsartan, this thesis is the first to describe the beneficial metabolic effects (i.e. improved insulin sensitivity) in obese hypertensive patients. However, to implement these results in treatment strategies for the hypertensive population, more research is necessary to unravel the underlying mechanisms in different metabolic tissues (e.g. skeletal muscle) and long-term health outcomes of therapy with the combinational drug sacubitril/valsartan.

The innovative aspect of the exercise training interventions, was the investigation of exercise training-induced effects on abdominal subcutaneous adipose tissue, since these studies have mainly been performed in rodents whereas human studies are scarce. Our results contribute to the knowledge and provide better insight in exercise training-mediated metabolic changes in abdominal subcutaneous adipose tissue. Furthermore, metabolic phenotyping at baseline makes it possible to stratify subjects into different subgroups and may improve the effectiveness of a particular intervention in a specific subgroup of the population \cite{12}. However, in this thesis we did not find clear evidence that metabolic phenotype at baseline affected exercise training-induced study outcomes. Therefore, before extrapolating our findings to a larger population, more research is necessary in larger study populations following different intervention strategies (e.g. nutritional, pharmacological as well as
prolonged exercise training interventions). Studies including more detailed metabolic phenotyping such as tissue-specific profiling are needed not only to identify individuals or subgroups at increased risk of developing metabolic diseases, but also to design optimized prevention and treatment strategies for specific subgroups of the population. These promising strategies will be further investigated by the current project team by performing human intervention trials including *in vivo* and laboratory analyses, performed via state-of-the-art research methodologies.
REFERENCES