Improving flexibility in substrate metabolism

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What is the main purpose of the research described in this thesis and what are the main results and conclusions?

This thesis aimed to investigate if a more pronounced fasting state during the night can improve metabolic health, with a special focus on substrate metabolism and liver glycogen. Normally, the body switches throughout 24 hours from glucose to fat oxidation and vice versa, with more glucose oxidation during the day and more fat oxidation during the night. This metabolic flexibility allows the body to use the nutrients which are available at the time, for example via meals. In individuals with overweight or obesity, and in individuals with metabolic diseases related to overweight such as non-alcoholic fatty liver disease (NAFLD), and type 2 diabetes, this flexibility in switching in substrate oxidation is diminished. Glycogen is a form of sugar stored in the liver and muscle. During the night, while fasting, glycogen is converted into glucose, which can be used as an energy source for the brain. The decrease of glycogen in the liver is potentially important for metabolic health, as low glycogen stores are known to stimulate the oxidation of fat. In this thesis, we wanted to investigate whether we can improve substrate oxidation by lowering hepatic glycogen levels via a pharmacological and lifestyle approach.

In **chapter 2**, the heterogeneity of type 2 diabetes, and the effects of different medication classes on insulin sensitivity and β-cell function were reviewed. Current treatment strategies are mainly based on lowering glucose levels; however, for an optimal treatment strategy, it is also necessary to treat the underlying cause of type 2 diabetes. From this review, we conclude that the choice of anti-diabetes medication can be better targeted to treat certain underlying causes. Especially medications that lowers body weight, such as SGLT2 inhibitors and GLP1-receptor agonists, should be used more, as obesity is a major underlying cause of type 2 diabetes. This review should raise the awareness in researchers and treating physicians of the heterogeneity within type 2 diabetes patients and how different aspects of diabetes can be addressed by various treatment options.

In **chapter 3** we investigated the effects of the pharmacological agent dapagliflozin, an SGLT2 inhibitor, in individuals with prediabetes. In patients with type 2 diabetes, SGLT2 inhibition has positive effects on blood glucose values and body weight. Because individuals with prediabetes have metabolic disturbances similar to the disturbances observed in patients with type 2 diabetes, SGLT2 inhibitor treatment might also have positive effects in individuals with prediabetes. We showed that treatment with an SGLT2 inhibitor in individuals with prediabetes increased fat oxidation, and improved muscle mitochondrial function. Therefore, we conclude that SGLT2 inhibitor treatment can be an effective treatment strategy in individuals with prediabetes, thereby reducing the risk to develop type 2 diabetes. The results

of this study set the stage for further research, investigating the benefits of SGTLT2 inhibition by treating individuals at an early stage in diabetes development, even before the disease manifests itself clinically.

Although treatment with a pharmacological agent is one way to improve metabolic health, it is also important to see what can be achieved with lifestyle changes. Therefore, in **chapter 4** we investigated if prolonging the overnight fast acutely by 6.5 hours beneficial effects on metabolic health in overweight individuals with NAFLD, and in lean individuals without NAFLD. We also investigated if liver glycogen stores were affected by extending the overnight fasting time. We prolonged the overnight fast by giving the last meal of the day at either 4.30 pm or 11 pm. We showed that prolonging the overnight fast acutely results in lower glucose oxidation and higher fat oxidation during the night. Furthermore, prolonging the overnight fast did not result in lower liver glycogen levels. Therefore, we conclude that acutely prolonging the overnight fast does stimulate fat oxidation, but this is probably not due to a decrease in liver glycogen. Considering the beneficial effects of an early dinner on nocturnal fat oxidation that was found in this study, together with other recent positive metabolic effects of restricting eating time (**chapter 5**), this reinforces current trends of time restricted eating, which can be easily applied in the general population.

In **chapter 5** we investigated if prolonging the overnight fast for 3 weeks has beneficial effects on metabolic health in patients with type 2 diabetes. Participants were instructed to adhere to a time-restricted eating protocol in which they could eat within a 10-hour time window with the latest meal completed no later than 6 pm or a control protocol in which they had to spread their food intake over at least 14 hours. We showed that time-restricted eating for 3 weeks resulted in lower 24-hour glucose oxidation, but no changes in fat oxidation. Furthermore, no differences were observed in liver glycogen. However, time-restricted eating resulted in improved fasting and 24-hours glucose levels. Therefore, we conclude that 3 weeks of time-restricted eating can be an effective treatment strategy to lower plasma glucose levels in patients with type 2 diabetes. This study identifies that time-restricted eating is an efficient and easy to implement lifestyle change that supports the treatment of type 2 diabetes.

Previously, it has been observed that older individuals with prediabetes have lower fat oxidation and higher glucose oxidation during the night compared to young lean individuals. In **chapter 6** we investigated which factor is responsible for this altered substrate oxidation during the night in some individuals. Therefore, we included participants from 10 different studies and divided them into 4 populations. We observed that individuals with overweight with or without type 2 diabetes had the lowest fat oxidation during the night, while overweight individuals with type 2 diabetes had the highest glucose oxidation. Furthermore, we observed that it is unlikely that age is the driving factor for the differences observed. However, BMI may be responsible for the differences observed in fat oxidation. Therefore,

we conclude that BMI might be a major determinant for low fat oxidation during the night. These results advance our understanding of the determinants of substrate oxidation during the night, an emerging field in metabolic research. Therefore, this study can be the basis for other researchers follow-up on this research.

What is the contribution of the results to the scientific community and societal challenges?

The prevalence of overweight and obesity is high and will be increasing in the upcoming years. Together with the rising prevalence of obesity, also the prevalence of diseases associated with obesity, such as NAFLD and type 2 diabetes, will increase. With the knowledge obtained in this thesis, the understanding of the metabolic disturbances observed in individuals with overweight with and without type 2 diabetes has significantly increased.

Further studies can extent on the results in this thesis by investigating the underlying cause for the observed differences in substrate metabolism between individuals, and exploring if medication or lifestyle interventions can stimulate fluctuations in liver glycogen, thereby improving metabolic health in individuals with obesity and related diseases, such as NAFLD and type 2 diabetes. With a better understanding of the underlying mechanisms causing metabolic disturbances in obesity and related diseases, better and more personalized treatments can be developed. As a result, the findings in this thesis may ultimately also contribute to reducing the costs related to health care.

For whom are the results interesting and of relevance?

The results presented in this thesis are of interest to different stakeholders. First, the results are of interest to other researchers working in the field of substrate metabolism, as knowledge on this topic was extended, especially with regard to fluctuations in substrate metabolism over the day and during the night in individuals with different metabolic disturbances. Furthermore, we investigated whether substrate metabolism can be improved by depletion of liver glycogen. With this knowledge, other researchers can develop follow-up studies to further investigate whether the depletion of liver glycogen can alter substrate oxidation during the night, and how such a depletion of glycogen can best be obtained. Ultimately, this knowledge can be used to develop better treatment strategies for the prevention of obesity and type 2 diabetes.

The insights into the role of pharmacological and lifestyle approaches to stimulate substrate metabolism are of interest to medical professionals such as general practitioners, endocrinologists, and dieticians. SGLT2 inhibitors are currently used in the treatment of type 2 diabetes, and to treat individuals with heart failure and chronic kidney disease with and without type 2 diabetes. We here showed that SGLT2 inhibitors have beneficial effects on

metabolism in individuals with prediabetes. Future research, and policy making should discuss if SGLT2 inhibitor treatment might also be used in individuals who are at risk for type 2 diabetes and if it can prevent the development of type 2 diabetes. Furthermore, medical professionals in direct contact with patients with type 2 diabetes can highlight the potential of time-restricted eating to lower blood glucose levels.

Finally, the results in this thesis are also of interest to the general public, especially for those who have obesity, NAFLD, or are at risk for, or diagnosed with type 2 diabetes, as they provide information about metabolic disturbances related to those diseases. This might stimulate individuals to improve their health by changing their lifestyle, for example by following a time-restricted eating protocol.

How can these target groups be involved and informed about the research results, so that the knowledge gained can be used in the future?

The results described in this thesis have been or will be shared with other researchers and medical professionals through publications in international peer-reviewed journals. Furthermore, the data have been or will be presented at national and international conferences. By publishing in journals and presenting at conferences, the results will be available for researchers, medical professionals and all others who are interested. In addition, the results will also be shared on websites, social media and during study participants' events. Participants who took part in the studies were invited to these participant events, in which the study results were presented.