

# Improving flexibility in substrate metabolism

Citation for published version (APA):

Veelen, A. H. (2023). *Improving flexibility in substrate metabolism: a pharmacological and lifestyle approach*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20230125av>

## Document status and date:

Published: 01/01/2023

## DOI:

[10.26481/dis.20230125av](https://doi.org/10.26481/dis.20230125av)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

## General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

[www.umlib.nl/taverne-license](http://www.umlib.nl/taverne-license)

## Take down policy

If you believe that this document breaches copyright please contact us at:

[repository@maastrichtuniversity.nl](mailto:repository@maastrichtuniversity.nl)

providing details and we will investigate your claim.

## SUMMARY

The prevalence of overweight and obesity is strongly increasing, and also the prevalence of diseases associated with obesity, such as non-alcoholic fatty liver disease (NAFLD), cardiovascular disease, and type 2 diabetes, is increasing. These metabolic diseases are characterised by altered 24-hour metabolism, in which the typical switch between high rates of carbohydrate oxidation in the postprandial state and high rates of fat oxidation in the fasted state is blunted. This leads to less pronounced carbohydrate and fat oxidation fluctuations over 24 hours. The research described in this thesis focuses on a better understanding of 24-hour substrate metabolism and investigates whether interventions that stimulate a more pronounced overnight fast can improve metabolic health.

Type 2 diabetes is a very heterogeneous disease that includes multiple metabolic dysfunctions characterized by hyperglycaemia, which is the result of various degrees of pancreatic  $\beta$ -cell failure and reduced insulin sensitivity. Despite the heterogeneity, there is no further classification of the disease based on the underlying cause of type 2 diabetes. Recently, Ahlqvist and colleagues suggested a new classification system of diabetes, which, at least partly, considers the heterogeneity of type 2 diabetes. In **chapter 2** we reviewed the heterogeneity of type 2 diabetes and discussed the new proposed classification system. Subsequently, we reviewed the effects of different second-line anti-diabetes medication classes on  $\beta$ -cell function, insulin sensitivity, and metabolism, and discussed the future treatment strategies based on the subgroups suggested by Ahlqvist *et al.* From this review, we conclude that current treatment strategies focus primarily on lowering blood glucose and HbA<sub>1c</sub> levels and on preventing end-organ damage. However, the new classification system gives an insight into the underlying cause of type 2 diabetes, and could therefore provide a basis for a more personalised treatment strategy focused not only on the consequences but also more tailored towards the cause of diabetes in an individual patient.

As mentioned above, one of the disturbances in type 2 diabetes is a disturbed 24h substrate metabolism. Sodium-glucose cotransporter 2 (SGLT2) inhibitor treatment results in the excretion of approximately 60 – 90 grams of glucose per day in patients with type 2 diabetes. It has been reported that SGLT2 inhibitor treatment results in lower 24-hour whole body carbohydrate oxidation and higher fat oxidation, as well as higher diurnal glucagon, free fatty acids, and  $\beta$ -hydroxybutyrate levels, and lower diurnal glucose and insulin levels. Furthermore, endogenous glucose production is higher as a compensatory effect of the loss of glucose via the urine. However, these effects have all been observed in individuals with type 2 diabetes, and the effects in individuals with prediabetes are largely unknown, yet relevant since individuals with prediabetes have metabolic disturbances similar to the disturbances observed in patients with type 2 diabetes. Therefore, in **chapter 3** we

investigated the effects of dapagliflozin, an SGLT2 inhibitor, on substrate metabolism and hepatic glycogen depletion in individuals with prediabetes. We showed that dapagliflozin treatment increased 24-hour and nocturnal fat oxidation and reduced carbohydrate oxidation, without affecting energy expenditure. Interestingly, dapagliflozin treatment did not affect overnight hepatic glycogen depletion, suggesting that predominantly gluconeogenesis is responsible for the increase in endogenous glucose production. Together, we conclude that SGLT2 inhibitor treatment can be an effective treatment strategy to improve metabolic health in individuals with prediabetes.

In addition to investigating the effects of a pharmacological agent on 24h substrate metabolism, lifestyle factors also affect energy and substrate metabolism. In fact, in our 24-hour society, most people tend to spread their food intake over a minimum of 14 hours, thereby decreasing their time to reach a true nocturnal fasting state and thus disturbing substrate metabolism. To investigate whether acutely prolonging the overnight fast would lead to improvements in substrate metabolism and metabolic health, we performed a proof-of-concept study in **chapter 4**. In this study, we investigated whether acutely prolonging the overnight fast by 6.5 hours would lead to more depletion of the hepatic glycogen stores, thereby increasing nocturnal fat oxidation in overweight individuals with NAFLD and in lean individuals without NAFLD. We provided the last meal of the day at either 4.30 pm or 11 pm, leading to an overnight fast of 9.5 hours and 16 hours. We showed that acutely prolonging the overnight fast resulted in higher nocturnal fat oxidation and lower nocturnal carbohydrate oxidation. However, these changes in substrate metabolism were not accompanied by changes in overnight hepatic glycogen depletion. Therefore, we conclude that acutely prolonging the overnight fast does stimulate nocturnal fat oxidation, but this is probably not due to a decrease in liver glycogen.

In **chapter 4**, the acute effects of a prolonged fast were investigated, but it is also important to investigate the longer-term effects of such intervention. Therefore, in **chapter 5**, we investigated the effects of prolonging the overnight fast for 3 weeks on metabolic health in patients with type 2 diabetes. In this study, we investigated whether repeatedly prolonging the overnight fast would lead to more depletion of the hepatic glycogen stores, thereby increasing nocturnal fat oxidation. 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 3 weeks of prolonging the overnight fasting time lowered 24-hour carbohydrate oxidation, but did not result in higher fat oxidation or changes in hepatic glycogen content. However, fasting and 24-hour glucose levels did improve. We conclude that repeatedly prolonging the overnight fast is effective to lower blood glucose levels, but does not alter fat oxidation or hepatic glycogen stores.

Previously, it has been observed that older individuals with prediabetes have lower nocturnal fat oxidation and higher carbohydrate oxidation when compared to young lean individuals. In **chapter 4** of this thesis, we also observed differences in nocturnal substrate metabolism in overweight individuals with NAFLD and in age-matched lean individuals without NAFLD. In **chapter 6** we combined the nocturnal substrate oxidation data from participants of 10 different studies and divided the participants into 4 populations depending on several participant characteristics. We observed that overweight individuals with or without type 2 diabetes had the lowest nocturnal fat oxidation, while overweight individuals with type 2 diabetes had the nocturnal highest carbohydrate oxidation. Furthermore, we observed that young and old lean individuals had similar nocturnal fat and carbohydrate oxidation. Next, we found a strong correlation between nocturnal fat oxidation and BMI. Therefore, we conclude that BMI might be a major determinant of low nocturnal fat oxidation.

In this thesis we investigated 24-hour and nocturnal substrate metabolism, specifically focused on whether a more pronounced overnight fast can improve metabolic health. In **chapter 7** we discussed all our findings and conclude that individuals with overweight or obesity have a disturbed 24-hour substrate metabolism and that this can be improved by pharmacological treatment and lifestyle intervention eliciting a more pronounced overnight fast.