

Liver substrate metabolism in non-alcoholic fatty liver

Citation for published version (APA):

Roumans, K. H. M. (2021). *Liver substrate metabolism in non-alcoholic fatty liver: role of hepatic lipid composition and hepatic glycogen measured by MR-techniques*. [Doctoral Thesis, Maastricht University]. Gildeprint Drukkerijen. <https://doi.org/10.26481/dis.20210915kr>

Document status and date:

Published: 01/01/2021

DOI:

[10.26481/dis.20210915kr](https://doi.org/10.26481/dis.20210915kr)

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

Take down policy

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

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

IMPACT

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

The aim of this thesis is to investigate how fat and glucose metabolism are changed in non-alcoholic fatty liver (NAFL) and how such changes contribute to impaired health. Specifically, this thesis focusses on liver fat, with special attention for the composition of the fat, and hepatic glycogen. Fats in the liver are composed of glycerol and fatty acids and the fatty acids can be classified based on the number of double bonds in saturated, mono-unsaturated and poly-unsaturated fatty acids. In general, saturated fatty acids are believed to be harmful to your health. Glycogen is the stored form of glucose and the liver is an important organ for this storage. This stored form of glucose can be used as energy source by the body when needed, for example during fasting when the body is not getting glucose from food. Liver glycogen could play an important role in determining whether body fat will be used or stored. In this thesis, liver fat content and composition and liver glycogen are determined by magnetic resonance spectroscopy methodologies. Magnetic resonance spectroscopy is a non-invasive technique that can be used to study the metabolism of organs such as the liver, without the need for taking biopsies.

In **chapter 2** the available methods to study the different routes that contribute to storage and disposal of fat in the liver were reviewed. It appeared that most studies are using techniques that require specific expertise and are costly. Therefore, the number of studies investigating the importance of these storage and disposal routes in the development of NAFL are limited, and even less is known about how diet can influence these routes.

One of the routes that can contribute to NAFL is the formation of fat from carbohydrates, called *de novo* lipogenesis. This newly formed fat is mainly saturated fat. In **chapter 3**, a new magnetic resonance spectroscopy technique was set-up to measure the fraction of the saturated, mono-unsaturated and poly-unsaturated fat in the liver. Once it was possible to measure these fat fractions in the liver, the relationship with *de novo* lipogenesis and liver insulin sensitivity could be studied. Liver insulin sensitivity indicates how well the liver responds to the hormone insulin, which is essential in maintaining normal blood sugar levels. It was shown that the higher *de novo* lipogenesis, the larger the fraction of saturated fat in the liver. Also, it was shown that in people with a large fraction of saturated fat in the liver, the sensitivity for insulin was reduced. A next step will be to investigate whether these relationships are causal. For example, does insulin sensitivity improve when we lower the amount of saturated fat in the liver by medication or diet?

In **chapter 4**, it was investigated if extending the overnight fast by 6.5 hours has beneficial effects on the health of volunteers with NAFL. This was done by eating the last meal of the day at 4.30 pm and comparing this to eating the last meal of the day at 11pm. Extending fasting time for a few hours each day has been shown before to have beneficial health effects. This could be due to fluctuations in liver glycogen. From our results, it appeared that people with NAFL are not sensitive to an extended overnight fast as liver glycogen did not change. Normally, fat oxidation is increased with fasting, but also this we did not see in these volunteers with NAFL. Furthermore, when the volunteers continued to extend their overnight fast for 5 days, no effects were seen on the amount and composition of liver fat. But why is the effect of fasting disturbed in people with NAFL? New research has to be performed to answer this question, which can lead to novel insights to improve health.

Another possible way to improve health and liver fat storage is by diet. There are indications that the amount of saturated fat in the diet and the glycemic index of the diet can play an important role. The glycemic index (GI) indicates how quickly food can increase blood glucose levels; the higher the GI of food, the quicker the blood glucose level increases. In **chapter 5** it was tested in overweight and obese volunteers whether a two-week diet low in saturated fat and GI would reduce liver fat storage when compared to a two-week diet high in saturated fat and GI. Indeed, it appeared that by only reducing the saturated fat and GI content of the diet for 2 weeks, liver fat storage decreased.

In addition to these results, it was shown in **chapter 6** that factors related to the way of measuring liver fat content with magnetic resonance spectroscopy and the calculations used can have a big influence on the amount of liver fat content that is measured. In **chapter 7**, a supplement, nicotinamide riboside, was used to improve health of overweight and obese people using some of the techniques that were also applied in abovementioned studies. It appeared that some health aspects, such as body composition, were improved, but that liver fat content and insulin sensitivity were unchanged.

What is the contribution of the results to science and societal challenges?

Obesity rates are extremely high worldwide and NAFL is frequently present in people with obesity. NAFL is the most common cause of chronic liver disease and can progress to more severe liver disease, but is also often accompanied by type 2 diabetes and cardiovascular disease. At present, knowledge about liver metabolism in people with NAFL and the health consequences of disturbed liver metabolism are limited.

The results of the research described in this thesis contribute to our understanding of human liver metabolism and its importance for human health. Based on the results of this

research new targets can be found that are important for improving health. Future studies can extend the findings presented in this thesis by investigating if lowering saturated fat in the liver and promoting fluctuations in liver glycogen by diet, exercise or medication can improve health of people with NAFL and related diseases, such as type 2 diabetes. Also, lowering dietary saturated fat and GI could be implemented by food industry, health care professionals, and government agencies in order to prevent the development of NAFL or treat NAFL and related diseases. Ultimately, this will contribute to reducing health care costs and relieving the pressure on the health care system.

For whom are the results interesting and of relevance?

The results and conclusions presented in this thesis are interesting for other researchers, who can set-up new studies further investigating the exact role of liver glycogen, saturated fat and *de novo* lipogenesis in NAFL and how these factors contribute to the development of NAFL related diseases. These studies can make use of the techniques described in this thesis, specifically the technique to specifically determine saturated fatty acids in the liver is new and enables us and other researchers in the field to perform follow-up studies. Ultimately, this knowledge could help in the prevention and treatment of NAFL and related diseases. In terms of prevention, this knowledge would be of interest for people with overweight and obesity, as these are at increased risk for developing NAFL. Specific lifestyle advice, such as minimizing dietary saturated fat and GI intake, may help this group at risk to keep liver fat content low and composition beneficial. Improving the quality of food products by the food industry in terms of saturated fat and GI could also aid in the prevention of fatty liver development. Next to this, knowledge from future studies building on our results can lead to the development of new drugs for the treatment of NAFL, thereby reducing the risk for progressed liver disease and the development of related diseases such as type 2 diabetes in people with NAFL.

Other researchers will be informed about the results described in this thesis through publications in scientific journals and presentations at national and international conferences. Results will also be shared on websites, social media and participant information events, thereby informing the people at risk for the development of NAFL and the people with NAFL or related diseases.