Nonalcoholic fatty liver disease

Citation for published version (APA):

Document status and date:
Published: 01/01/2021

DOI:
10.26481/dis.20210531tm

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.uml.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 Paragraph

During the past century healthcare has rapidly evolved, for instance by making many of the old infectious diseases curable. However, new medical challenge have emerged due to growing burden of metabolic diseases associated with overweight, obesity and unhealthy lifestyle. Based on extensive research in the last two decades it became clear that nonalcoholic fatty liver diseases (NAFLD) is associated with a general metabolic dysfunction caused by this unhealthy lifestyle. Because of the ongoing obesity epidemic NAFLD has become the main cause of chronic liver disease in the Western world with a prevalence of 25% in the adult population. In case no actions are taken this number will keep rising rapidly. The world health organisation (WHO) has issued the protection of people from unhealthy food and substances as one of 13 challenges for the following decade, hopefully limiting the rise of metabolic disease including NAFLD. To date, the social and economic burden of NAFLD is rising rapidly. The annual NAFLD associated direct costs (costs associated to medical care) are estimated to be $103 billion ($1,613 per patient) in the United States and €35 billion (from €354 to €1,163 per patient) in Germany, Italy, United Kingdom and France combined. In this analysis only direct medical costs were included, medical costs associated with extrahepatic comorbidities and indirect costs which are related to work productivity loss were not taken into account. Furthermore, the societal cost related to loss of quality-adjusted life years due to NAFLD is important. To limit the social and economic burden, high-quality research focussing on NAFLD is necessary. In this thesis we aimed to gain more insight into the complex pathophysiology of NAFLD.

NAFLD is characterised by excessive fat accumulation in the liver which is in the majority of the cases caused by an unhealthy lifestyle. It is estimated that around 25% of NAFLD patients develop chronic inflammatory state referred to as nonalcoholic steatohepatitis (NASH). NASH patients are more likely to develop hepatic fibrosis, cirrhosis or hepatocellular carcinoma (HCC). Based on previous research we known that especially NAFLD patients with hepatic fibrosis have an increased risk for liver and non-liver related mortality. Today, the exact pathophysiology of NAFLD is not completely understood and it remains unclear why some but not all NAFLD patients develop NASH, hepatic fibrosis, cirrhosis or HCC. Over the last two decades NAFLD pathophysiology has been extensively studied in animal models and humans. Several factors have been identified to be involved in NAFLD pathophysiology including dietary habits, genetic predisposition, bile acid regulation, gut microbiome and disturbance in glucose and lipid metabolism. In this thesis we investigated less frequently studied but therefore not less important factors potentially involved in NAFLD pathophysiology. Alterations in intestinal permeability, brown adipose tissue
(BAT) activity and muscle fat fraction (myosteatosis) may contribute to NAFLD development and progression and were therefore studied. Increased intestinal permeability is believed to induce NAFLD development and progression by, among others, translocation of bacterial products from the gut to the liver. BAT has the unique capacity to burn energy by generating heat. However, loss of BAT activity may enhance NAFLD development. Finally, myosteatosis is a cause and consequence of insulin resistance, a factor strongly associated with NAFLD development and progression. Therefore, myosteatosis may prove to be an ideal marker for NAFLD presence and severity. Further studies unravelling the complex pathophysiology of NAFLD, to which this thesis has contributed, are urgently needed in order to develop diagnostic markers and new therapeutic options.

Dietary interventions and lifestyle modifications are generally considered as first-line therapy for NAFLD. To reduce the amount of hepatic steatosis, inflammation and fibrosis in NAFLD patients, 5-10% bodyweight reduction needs to be obtained. Nevertheless, in clinical practice, most patients do not achieve sustained weight loss even with multidisciplinary interventions. Therefore, pharmacological add-on therapy is needed for an effective treatment. Many pharmacological agents for the treatment of NAFLD are currently being explored in clinical trials. Up to now, not a single pharmacological therapy has been approved for NAFLD and the effectiveness of current agents under investigation is low. NAFLD is a heterogeneous liver disease, and different pathophysiological factors may lead to the same histological and clinical phenotype. Dysfunction along the gut-liver axis or adipose tissue-liver axis may only be present in a subset of NAFLD patients. More detailed information on these NAFLD subgroups is needed to develop future personalized therapeutic approaches. The investigated extrahepatic factors in NAFLD patients studied in this thesis, that is, the gut, BAT and muscle, may contribute to a more detailed phenotyping of NAFLD patients. In future, this may result in new therapeutic options in a subgroup of NAFLD patients because it is unlikely that a “one size fits all approach” will be successful for the treatment of all NAFLD patients. In addition, we showed that most, but not all NAFLD patients have an increased intestinal permeability compared to healthy control subjects. In addition, NAFLD patients with clinical significant hepatic fibrosis have an increased colon permeability compared to NAFLD patients without fibrosis. It is therefore expected that upcoming therapies to reverse gut-liver axis dysfunction, such as new generations of probiotics, will be more effective in NAFLD patients with increased intestinal permeability. Similarly, the reduced BAT activity in NASH mice may be resolved by future pharmacological therapies to restore BAT function. Recovery of BAT function may reduce NAFLD progression to NASH. However, these observations could not yet be translated to the human situation as BAT activity is difficult to measure in humans. New pharmacological treatments are urgently needed, as failure of the present available interventions
increases the risk of NAFLD progression to end-stage liver disease. In such cases a liver transplantation is the only remaining therapeutic option. Since NAFLD prevalence is rising worldwide, NAFLD will become the leading indication for liver transplantation further increasing its social and economic burden on society.

In conclusion, this thesis will contribute to a better understanding of the complex pathophysiology of NAFLD. This will lead to new mechanistic research in the field of NAFLD which may result in new diagnostic and therapeutic options, needed to prevent a further rise in the NAFLD related social and economic burden. Furthermore, this thesis underlines that NAFLD is a multisystem disease with several extrahepatic manifestations for which a personalised multidisciplinary interventions are needed.
References


