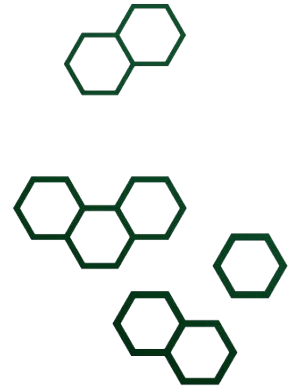
Non-alcoholic fatty liver disease. Mind the gaps



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This thesis focussed on the highly prevalent non-alcoholic fatty liver disease (NAFLD). NAFLD is a lifestyle related disease, associated with overnutrition and a sedentary lifestyle. This lifestyle is leading to an escalating global epidemic of overweight and obesity, which leads not only to NAFLD, but also to other serious non-communicable diseases, including diabetes mellitus, cardiovascular disease, hypertension and stroke and specific types of cancer.[1] These diseases undermine health, shorten life expectancy and cause enormous suffering, disability and economic costs.[2]

Currently, the global prevalence of NAFLD of more than 25%. The number of patients diagnosed and referred with NAFLD is expected to rise further in the near future. The term NAFLD comprises both simple steatosis and non-alcoholic steatohepatitis (NASH). Simple steatosis is a more benign form of fat accumulation in the liver, present in the majority of patients. NASH is a chronic inflammatory state that develops in about 30% of NAFLD patients and leads to an overall increase in morbidity and mortality due to the progression to fibrosis, cirrhosis and hepatocellular carcinoma (HCC). The complex pathophysiology of NAFLD is multifactorial and not yet completely clear. Furthermore, at this moment there are limited therapeutic options available for NAFLD. Lifestyle changes, including diet and physical exercise are considered the mainstay treatment for the majority of patients with NAFLD.[3,4] However, it is common knowledge that sustained weight loss is difficult to achieve and especially difficult to maintain. Therefore, other treatment options like pharmacotherapy also need to be considered as an add-on therapy. Up to now no drug has been approved for NASH by regulatory agencies, and any drug treatment is still off-label.

In case lifestyle changes and other interventions failed and end-stage liver disease has developed, a liver transplantation can be considered. It is thought that NAFLD will probably become the leading indication for liver transplantation due to the still rising prevalence of NAFLD.[5] Additionally, the rapidly growing prevalence of NAFLD will also impact the pool of potential donors, as it is expected that a higher proportion of potential liver donors will have NAFLD and might be declined for liver transplantation use. Not only the fact that NAFLD can shrink the pool of potential liver donors, but also patients developing recurrent NAFLD after liver transplantation is putting a strain on the system.

In order to counter these alarming trends, a better knowledge and understanding of factors associated with progressive disease in NAFLD is needed. These numbers underline the importance of properly routing NAFLD patients to the right healthcare professional, meaning referral of patients at risk of progressive liver disease to secondary care and follow-up of low-risk NAFLD patients in primary care, to lower both the economic and disease burden of this disease. In this thesis, we aimed to gain more insight the pathophysiology, non-invasive diagnostic options and the bridge to primary care, to improve healthcare.
Several pathophysiological factors were studied in this thesis, namely defenestration of liver sinusoidal endothelial cells, the role of ferritin and myosteatosis. Even though, interesting results were found, they do not explain the entire pathophysiology of NAFLD. This has to do with the fact that pathophysiology of NAFLD is multifactorial. Due to this complex interplay, such as the involvement of several organs and inter-individual variation in disease presentation, human research on NAFLD is important. A well-characterised cohort of NAFLD patients with bio-sampling, which can be followed over a longer period of time, can help to get a better and more complete understanding of the natural disease course and factors that influence the development of progressive disease. However, this type of clinical research is very demanding, therefore it is important to supplement these kind of studies with research, both human and animals studies, focussing on specific mechanisms. In this manner, the longitudinal studies could be used to validate findings and in this way benefit scientific impact.

To date, liver biopsy is the most sensitive test for detecting and staging NAFLD. So far, it is the only reliable method to diagnose NASH.[3] Due to its invasiveness, high costs and risk of complications, liver biopsy is not a diagnostic method that is suitable to apply in large populations or for monitoring the disease. In clinical practice, only subjects at high risk of NASH, usually based on elevated liver enzymes measured in the blood, will be considered to undergo a liver biopsy. This may lead to underdiagnoses of NASH, since a significant part of NASH patients do not have elevated liver enzymes. Even though, fibrosis stages 1-4 were found to be the strongest predictor for disease-specific mortality in NAFLD, there is an urgent need for non-invasive methods to detect NASH among the general population, since NASH is a recognized driver of liver fibrosis and fibrosis progression. A non-invasive diagnostic tool for NASH could benefit both healthcare and research purposes. This thesis provided an extensive overview of

the available non-invasive diagnostics studied in recent years. We showed that several scores that combined different non-invasive markers showed promising results. However, none of the markers or combination of markers identified, was able to differentiate NASH from simple steatosis and a non-invasive marker for NASH is therefore not yet available in clinical practice. Due to the complexity of NAFLD, it is likely that a score consisting of multiple parameters may be able to diagnose NASH in the future. It would be of value to use -omics approaches to identify interesting parameters that could possibly be used for non-invasively diagnosing NASH. Omics aim at the collective characterization and quantification of pools of biological molecules that translate into the structure, function and dynamic of an organism or organisms. The goal is to find an affordable diagnostic tool that includes parameters that both easily as well as reliably diagnose NASH non-invasively. Once implemented in clinical care, it should enable diagnosing and monitoring of large groups, so the proper guidance/treatment can be given to the right patients. Finding and implementing such a tool would be of great benefit especially for general practitioners (GPs). Due to the high prevalence but low severity of NAFLD in the majority of patients, GPs, as gatekeepers of our health care system, are confronted with large numbers of NAFLD patients. However, until a non-invasive diagnostic tool is available, GPs need to be trained to identifying patients at risk of progressive liver disease for secondary care referral. Furthermore, adequate education on the follow-up and treatment of low-risk patients should be provided, taking into account cost-effectiveness. This thesis showed that there is a need for increased awareness and knowledge on NAFLD in the field of primary care. Until non-invasive diagnostics, to enable early diagnosis of NASH, are implemented in clinical care, the flowcharts provided by the EASL and BASL guideline should be used in primary care to help route patients to the right healthcare professional.[3,6]

In conclusion, this thesis proposes possible factors that play a role in the pathophysiology of NAFLD, these findings can provide foundation for future mechanistic research. Furthermore, we have provided an overview of the non-invasive diagnostics of NASH studied over the years. Even though a non-invasive diagnostic tool is not yet available in clinical healthcare, our overview has shown that combining various parameters is necessary in the development of a non-invasive diagnostic tool for NASH. This can provide leads for developing a test that can be implemented in clinical practice and can be used in future studies on the identification of risk factors for progressive disease.

Finally, this thesis has shown the importance of a collaboration between hepatologists and primary care physicians to guide patients to the right healthcare professionals, especially as the numbers of NAFLD patients are expected to rise even further the coming years.
A great effort to increase application of public health and interventions to reduce prevalence of poor diet and insufficient physical activity, increase awareness of NAFLD and promote the use of flowcharts until a non-invasive diagnostic tool is available, could substantially reduce the human and economic costs of this disease.

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