Interventions targeting hepatic and cardiovascular complications of metabolic syndrome

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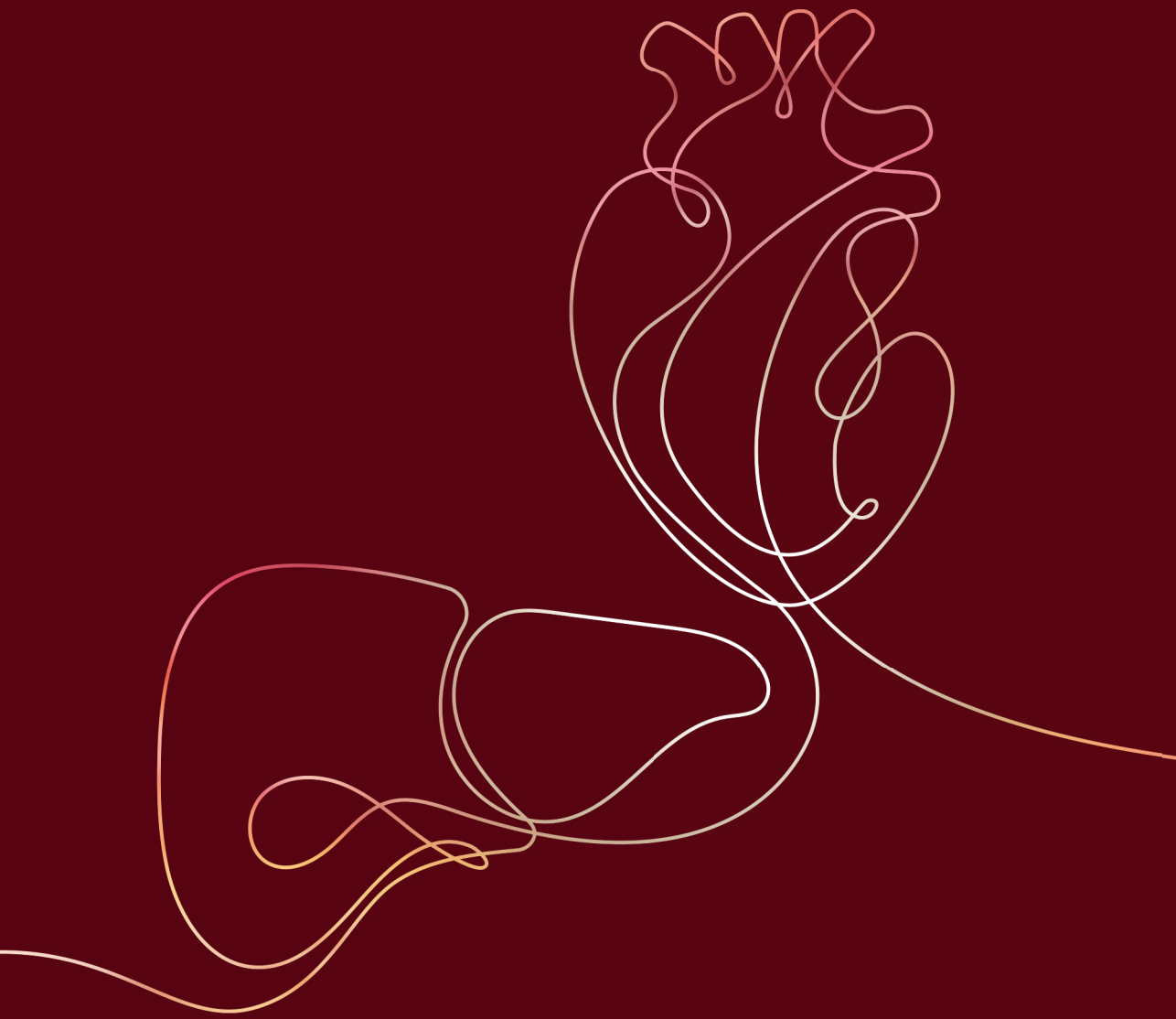

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General Discussion

The increasing prevalence of metabolic syndrome and associated complications calls for different approaches than lifestyle interventions alone. The use of preclinical models allows for the investigation of molecular and pathophysiological mechanisms that can be targeted for pharmacological intervention. This thesis described a variety of preclinical studies that focus on (I) metabolic dysfunction-associated steatotic liver disease (MASLD) and (II) atherosclerosis with the goal of better understanding, preventing and treating complications that result from metabolic overload.

1. Metabolic syndrome: focus on MASLD

Implementation of lifestyle changes remains the preferred approach for preventing development of metabolic complications, yet often prove difficult to sustain and may result in weight cycling, which is generally considered unfavorable for effectively reducing such complications. Nevertheless, literature on weight cycling remains controversial, largely due to the absence of a standardized definition of weight cycling, which complicates comparisons across studies. Therefore, in **Chapter 2**, we evaluated the effects of repeated weight cycling under controlled conditions in obese Ldlr-/-.Leiden mice. Contrary to common assumptions, we found that repeated weight cycling did not have negative effects and instead we observed improvements in parameters such as plasma lipids and hepatic inflammation when compared to a continuous diet high in fat and sugar. These results challenge the assumption that repeated weight cycling is inherently harmful. Our study provides mechanistic insights into how metabolic flexibility may be preserved despite fluctuations in body weight. Furthermore, these results raise questions about the clinical emphasis on weight stability as a primary goal, and whether a more nuanced approach that considers metabolic markers rather than weight alone might be more appropriate. Although the controlled environment of preclinical studies is advantageous for isolating weight cycling as a single variable, it also limits the extent to which findings can be generalized to real-world scenarios. In humans, metabolic health is influenced by a complex interplay of factors including for example physical activity levels, psychological well-being, genetic polymorphisms, but also pharmacological treatments. These elements are excluded in preclinical studies but may influence the effects of weight cycling in less predictable ways. Nevertheless, by isolating weight cycling, this study contributes valuable mechanistic insight and supports the notion that the metabolic consequences of weight cycling are context-dependent rather than universally detrimental.

While weight cycling may offer transient metabolic benefits, it remains less favorable than adapting and maintaining a consistent healthy lifestyle. However, when lifestyle interventions are no longer feasible, pharmacological interventions

become a necessary step to improve metabolic health and mitigate associated complications. For treatment of the hepatic manifestation of metabolic syndrome, i.e. MASLD, several therapeutic strategies have been developed. Although many of these interventions show significant benefits in reducing hepatic steatosis and inflammation, they frequently fail to reverse hepatic fibrosis that manifests in later stages of the disease. Notably, several compounds that demonstrated promising anti-fibrotic effects in preclinical studies have ultimately failed in clinical trials. Importantly, preclinical models should not only replicate end-stage pathology but also reflect the dynamic progression of MASLD to ensure translational relevance. Inadequate disease modeling may lead to false-positive outcomes during drug development. The use of Ldlr-/-.Leiden mice on a diet high in fat and sugar content closely reflects human MASLD, replicating key metabolic features such as obesity, insulin resistance, hyperlipidemia, liver histopathology and underlying metabolic pathways[1]. In a previous study using the same model-diet combination, a gene expression signature consisting of 232 differentially expressed genes (DEGs) was identified that reflected profibrotic processes prior to the onset of histological fibrosis[2]. In **Chapter 3**, we demonstrated that short-term interventions changed this gene signature in response to three distinct experimental and registered drugs and accurately predicted their long-term efficacy on histological fibrosis. This approach enables rapid screening of novel therapeutic candidates for MASLD-related fibrosis in short-term studies, offering a powerful tool to accelerate drug development and optimize combination therapies. To build on these findings, future research should investigate whether this fibrogenic gene signature can differentiate between compounds that merely halt fibrosis progression and those that actively reverse it, a distinction that holds significant clinical relevance for long-term outcomes in patients with MASLD.

Recent advances have been made in targeting fibroblast growth factor 21 (FGF21) signaling, showing great potential in not only mitigating hepatic steatosis and inflammation, but fibrosis as well. Mechanistically, the hepatokine FGF21 acts through the receptor complex comprised of the FGF receptor 1c (FGFR1C) and β-klotho (KLB), yet its beneficial effects on obesity, blood sugar and plasma lipids are limited by rapid clearance from the circulation. In **Chapter 4**, we evaluated the therapeutic potential of bFKB1, a novel antibody with a long half-life that was designed to mimic FGF21 by specifically targeting and activating both FGFR1C and KLB. This targeted approach led to notable metabolic improvements in diet-induced obese Ldlr-/-.Leiden mice, including reduced adipocyte size and adipose tissue inflammation and induction of white adipose tissue browning. In the liver, bFKB1 significantly alleviated steatosis and inflammation, and although fibrosis remained unchanged, collagen deposition was reduced and profibrotic transcriptional activity broadly suppressed. Additionally, bFKB1 markedly decreased atherosclerotic plaque size and severity.

The findings from this study highlight the potential of targeting FGF21 signaling as a systemic strategy for treating MASLD and broader metabolic syndrome, with beneficial effects extending beyond the liver to adipose tissue and vascular health. Currently, several FGF21 analogues are undergoing clinical evaluation for the treatment of MASLD. Notably, the bivalent Fc-FGF21 analogue efruxifermin demonstrated both MASH resolution and fibrosis improvement in the phase 2b HARMONY trial[3] and results of the phase 3 SYNCHRONY trials are expected in the upcoming years. Similarly, pegozafermin, a glycopegylated FGF21 analogue, showed significant efficacy in reducing hepatic steatosis and fibrosis in its own phase 2b study[4] and has now progressed into phase 3 evaluation in the ENLIGHTEN program (NCT06318169). In light of our own study, which demonstrated broad metabolic benefits of an FGF21 mimetic, these clinical results further support FGF21 as an interesting strategy to address metabolic complications, with particular relevance to MASLD.

In recent years, glucagon-like peptide-1 (GLP-1) receptor agonists, such as semaglutide, have gained significant attention beyond their initial indication for type 2 diabetes. Initially approved for glycemic control, semaglutide was later recognized for its potent weight-lowering effects, ultimately becoming one of the first pharmacological agents approved for obesity treatment. This shift has catalyzed a surge in research exploring its broader metabolic effects, including those on MASLD. By mimicking GLP-1, semaglutide enhances insulin sensitivity, delays gastric emptying and promotes satiety, mechanisms that all contribute to its efficacy in weight reduction and metabolic regulation. **Chapter 5** of this thesis explored the effects of semaglutide in diet-induced Ldlr-/-.Leiden mice. In this model, while semaglutide had strong beneficial effects on hepatic steatosis and inflammation, it failed to reduce hepatic fibrosis after 12 weeks of intervention. However, more detailed digital pathology revealed significant beneficial effects of semaglutide on the degree of collagen fiber reticulation, indicative of reduced complexity of the fibrotic network. Additionally, we found that semaglutide predominantly reversed expression of genes involved in profibrotic processes. Possibly, a longer treatment duration would have resulted in fibrosis improvements as well. Interestingly, during the course of carrying out and writing this thesis, semaglutide received accelerated approval from the U.S. Federal Drug Administration (FDA) for the treatment of patients with MASH with moderate-to-advanced fibrosis. This decision was based on the ongoing phase 3 ESSENCE trial (NCT04822181), which demonstrated significant histological improvements, including resolution of steatohepatitis and reductions in hepatic fibrosis[5].

Although semaglutide and other GLP-1 receptor agonists are highly effective in promoting weight loss and improving metabolic parameters, concerns have been raised regarding their long-term effects. In particular, the rapid and substantial

weight reduction often includes a loss of lean body mass, which raises concerns about the preservation of muscle health over time. To address this, **Chapter 6** explored the hypothesis that combining semaglutide treatment with exercise could mitigate muscle loss while retaining the metabolic benefits. To this end, we performed a comprehensive study in Ldlr-/-.Leiden mice in which we studied the effects of combining semaglutide with exercise on metabolic, adipose, muscle, liver and vascular parameters. Combination treatment reduced fat mass and lean mass as well, but to a lesser extent than semaglutide intervention alone. Interestingly, combination treatment significantly improved muscle function and diameter of gastrocnemius myofibers, while these parameters were not affected by semaglutide or exercise alone. Furthermore, the combination of semaglutide and exercise improved insulin sensitivity, plasma lipids, adipose tissue inflammation, liver steatosis and inflammation and atherosclerotic lesion area. These results were further substantiated at the transcriptomics level, with synergistic effects of combination intervention on the activation of pathways involved in mitochondrial function, glucose metabolism and inflammation resolution. The results from this study demonstrate that semaglutide-induced weight loss should be combined with exercise in order to counteract negative effects on muscle. This study provides compelling evidence that lifestyle interventions can enhance efficacy of pharmacological interventions and mitigate their adverse effects. This approach should therefore be considered to optimize outcomes in patients with metabolic syndrome.

Statins are indicated for the primary and secondary prevention of CVD, owing to their function in inhibiting the rate-limiting enzyme in the cholesterol synthesis pathway. Consequently, they are indicated for patients with one or more CV risk factors, such as dyslipidemia, diabetes or hypertension. Moreover, statins not only lower CV mortality but reduce all-cause mortality as well[6]. Therefore, in **Chapter 7**, we investigated how atorvastatin affects MASLD development and explored underlying mechanisms. In APOE*3-Leiden mice on a Western-type diet, atorvastatin significantly improved hepatic steatosis, inflammation and fibrosis. Atorvastatin strongly reduced the formation of cholesterol crystals, thereby reducing induction of the NLR family pyrin domain containing 3 (NLRP3) inflammasome. Elevated hepatic cholesterol levels are known to exert a pro-inflammatory effect, which contributes to MASLD progression[7,8]. The strong anti-inflammatory effects of atorvastatin were further substantiated at the transcriptomics level. Atorvastatin is widely used in the clinic to improve dyslipidemia and reduce CV risk and with this study we provide rationale for statins to be prescribed to reduce existing MASLD and additional cardiovascular risk, and to prevent progression into MASH in a broad population of dyslipidemic patients. Furthermore, recent meta-analyses in MASLD patients underscore the beneficial effects of statin use on liver enzymes and liver histology[9] as well as in reducing overall and cancer-related mortality[10].

1.1 Recent advances in the treatment of MASLD

During the time the experiments and writing of this thesis were carried out, one compound was approved for the treatment of MASLD and MASLD-associated fibrosis. Resmetirom is a selective thyroid hormone receptor β (THR-β) agonist that enhances mitochondrial β-oxidation, which reduces lipid accumulation in the liver while concomitantly modulating inflammatory and fibrotic pathways. In the pivotal MAESTRO-NASH phase 3 trial (NCT03900429), resmetirom intervention resulted in resolution of MASH and at least one stage improvement in hepatic fibrosis compared to placebo[11]. As a result, the drug received approval by the U.S. FDA in March 2024 and by the European Medicines Agency (EMA) in August 2025, making it the first drug approved for treatment of MASLD. Resmetirom has also been tested in Ldlr-/-.Leiden mice, where it reduced plasma LDL-C and MASLD[12], in line with the MAESTRO-NASH trial and indicating the translational value of the model.

The therapeutic landscape for MASLD is rapidly evolving, with several promising compounds now emerging. For example, the fatty acid synthase inhibitor denifanstat is currently under investigation in the FASCINATE-3 phase 3 clinical trial (NCT06594523). Phase 2 data on denifanstat have shown promising effects on hepatic steatosis, inflammation and fibrosis[13]. Furthermore, as previously mentioned, additional compounds targeting distinct pathways are in development as well, including FGF21 analogues and GLP-1 analogues. Moreover, dual and triple GLP-1/GIP (glucose-dependent insulinotropic polypeptide)/glucagon receptor agonists are gaining traction as next generation pharmacological interventions, building on the success of single GLP-1 analogues and expanding their potential to address MASLD alongside their weight-reducing benefits. Icosabutate, a FFAR1/FFAR4 agonist, has also shown encouraging anti-fibrotic effects in the phase 2b ICONA trial, with significant improvements in liver fibrosis observed through both conventional and AI-assisted histological assessments, despite not meeting its primary endpoint[14]. With growing insights into the pathophysiology of MASLD, new therapeutic targets continue to be identified. The approval of resmetirom and semaglutide, the advancement of denifanstat and the repurposing of GLP-1 analogues represent major milestones in reshaping the treatment landscape for MASLD.

2. Metabolic syndrome: focus on atherosclerosis

Cardiovascular disease remains the primary cause of mortality worldwide and is the main cause of death in patients with MASLD[15]. There is a strong association between intensive lipid lowering and better CV outcomes[16,17], which has resulted in the "lower the better" principle for reducing LDL-C and non-HDL-C. This principle is supported by extensive evidence showing that each incremental reduction in atherogenic

lipoproteins, particularly non-HDL-C, is associated with a proportional decrease in cardiovascular risk, without a clear lower threshold beyond which no further benefit is observed[18]. Evidence from the ODYSSEY OUTCOMES trial demonstrated that patients with a recent acute coronary syndrome and that achieved very low LDL-C levels by intervention with alirocumab and statins had significantly lower incidence of major adverse CV events compared to patients on statins alone[18]. Currently, there are many lipid-lowering agents that, alone or in combination, result in substantial lipid lowering. However, it should be kept in mind that there is considerable inter-patient variability in response to these various agents, therefore necessitating close monitoring of treatment efficacy. Low-intensity statin intervention is the first line of approach in managing plasma lipids. However, many patients develop adverse effects or do not reach target levels. In this case, high-intensity statins, other pharmacological agents or combination therapies should be considered.

Since the discovery of PCSK9 as regulator of LDL receptor membrane expression, strong advances have been made to target this process and improve plasma lipids. Currently, the PCSK9 inhibitors evolocumab and alirocumab are in clinical use and reduce LDL-C levels by ~60%[19–22]. These monoclonal antibodies are, however, relatively expensive, need to be injected every 2 or 4 weeks and therefore application to a large range of patients is less feasible. In **Chapter 8**, we evaluated the effects of a novel PCSK9 inhibitory peptide alone and in combination with evinacumab in APOE*3-Leiden.CETP mice. Treatment with this PCSK9 inhibitory peptide alone and with the ANGPTL3 inhibitor evinacumab resulted in significant improvements in plasma cholesterol and triglycerides, which resulted in an almost complete nullification of atherosclerosis development in these mice. This peptide-based approach offers a more cost-effective and scalable approach to PCSK9 inhibition. Other approaches to PCSK9 inhibition show similar beneficial effects. The small interfering RNA molecule inclisiran inhibits PCSK9 synthesis and has been shown in phase 3 clinical trials to lower LDL-C levels by approximately 50%[23]. Inclisiran is administered via subcutaneous injection with a follow-up dose after three months and subsequently maintenance doses every six months. Its long-acting profile makes it a promising alternative for more classical PCSK9 monoclonal antibodies. The primary outcomes of two clinical trials (NCT03705234 and NCT05030428) are expected in 2026 and 2027, in which will be investigated whether LDL-C reduction with inclisiran translates into fewer major adverse CV events in patients with CVD. In this context, both the PCSK9 inhibitory peptide described here and inclisiran exemplify emerging, cost-effective alternatives to monoclonal antibodies, with the potential to broaden access to PCSK9-targeted therapies for a wider patient population.

In **Chapter 9**, we evaluated the mechanism of action underlying the lipid-lowering effects of obicetrapib and ezetimibe, and how these effects influence atherosclerosis development. Given its central role in cholesterol metabolism, cholesteryl ester

transfer protein (CETP) represents an interesting target for therapeutic intervention. Historically, several CETP inhibitors, including anacetrapib, torcetrapib, dalcetrapib and evacetrapib, failed to reach clinical application due to limited efficacy or adverse side effects[24–27]. Obicetrapib is a next-generation CETP inhibitor that has demonstrated strong lipid-lowering effects in both clinical settings and here in APOE*3-Leiden. CETP mice. However, the precise mechanism of action driving these effects remained incompletely understood. Our findings show that obicetrapib, in combination with ezetimibe, reduces non-HDL-C levels by upregulating hepatic LDL receptor expression, thereby enhancing VLDL clearance from the circulation. This synergistic action contributes to a more favorable lipid profile and effectively slows atherosclerosis progression. Notably, when added to atorvastatin therapy, this combination induces aggressive lipid lowering, leading to regression of advanced atherosclerotic lesions and even curing pre-existent lesions. The latter is of particular importance in the CVD patient population, as treatment is typically initiated after atherosclerosis is already in advanced stages. As mentioned before, obicetrapib has been shown in the clinic to improve lipid levels[28–32] and is currently under investigation for treatment of dyslipidemia and CVD. It is being studied in a phase 3 clinical trial (NCT05202509) to assess its potential to reduce occurrence of major cardiovascular events in patients with atherosclerotic CVD[33]. Additionally, the phase 3 REMBRANDT trial (NCT06305559) is investigating the effects of obicetrapib and ezetimibe on coronary plaque characteristics in at-risk patients[34]. In the APOE*-Leiden.CETP mouse model, the lipid-lowering effects of obicetrapib and ezetimibe closely reflected those observed in humans, suggesting that similar benefits may be expected in these ongoing clinical studies. Results from these trials are anticipated in the coming years.

3. Concluding remarks and future perspectives

Despite significant progress in understanding the pathophysiology of MASLD and CVD, many patients remain at (residual) risk. The studies presented in this thesis highlight the need for strategies that combine lifestyle modifications with pharmacological interventions or multiple pharmacological interventions to address the complex and multifactorial nature of metabolic syndrome. Recent therapeutic advances in the field of MASLD, such as FGF21 analogues, GLP-1 receptor agonists and THR-β agonists highlight the growing recognition of the liver as a central organ in metabolic regulation. In parallel, the development of more accessible PCSK9 inhibitors and more efficacious and safe CETP inhibitors offers promising strategies for mitigating CV risk as well.

Preclinical models that accurately reflect disease development as it is observed in humans are particularly valuable for investigating the mechanisms of action behind novel (combinations of) pharmacological interventions. We have explored several strategies to help improve liver as well as cardiovascular health in the context of metabolic syndrome. Novel strategies that aim at preventing or treating MASLD or atherosclerosis should not be limited to the liver or vasculature only, but rather should focus on dysmetabolism and inflammation across multiple organ systems that affect overall metabolic status. Preclinical studies are ideal to study drugs more mechanistically and holistically, taking into account the body as an integrated system rather than isolated parts of the whole. Moreover, existing drugs developed for other indications could be repurposed towards metabolic complications, which for example we did by using statins for treatment of MASLD. More attention should also be paid to combining pharmacological interventions. Targeting complementary mechanisms with different drugs, such as obicetrapib with ezetimibe, can enhance efficacy and result in more aggressive lipid lowering. Nevertheless, despite these pharmacological advances, lifestyle changes remain essential for achieving sustained benefits and mitigating long-term adverse effects, such as sarcopenia.

This thesis described multiple intervention strategies with potential to treat the hepatic and cardiovascular complications of metabolic syndrome. With metabolic syndrome increasingly recognized as a systemic condition rather than a collection of isolated components, the field is now well-positioned to pursue more integrated and targeted therapeutic approaches. However, continued research is essential to refine these strategies, address remaining knowledge gaps, and ensure that emerging treatments translate into meaningful, long-term benefits for patients with MASLD and cardiovascular disease.

4. References

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