Interventions targeting hepatic and cardiovascular complications of metabolic syndrome

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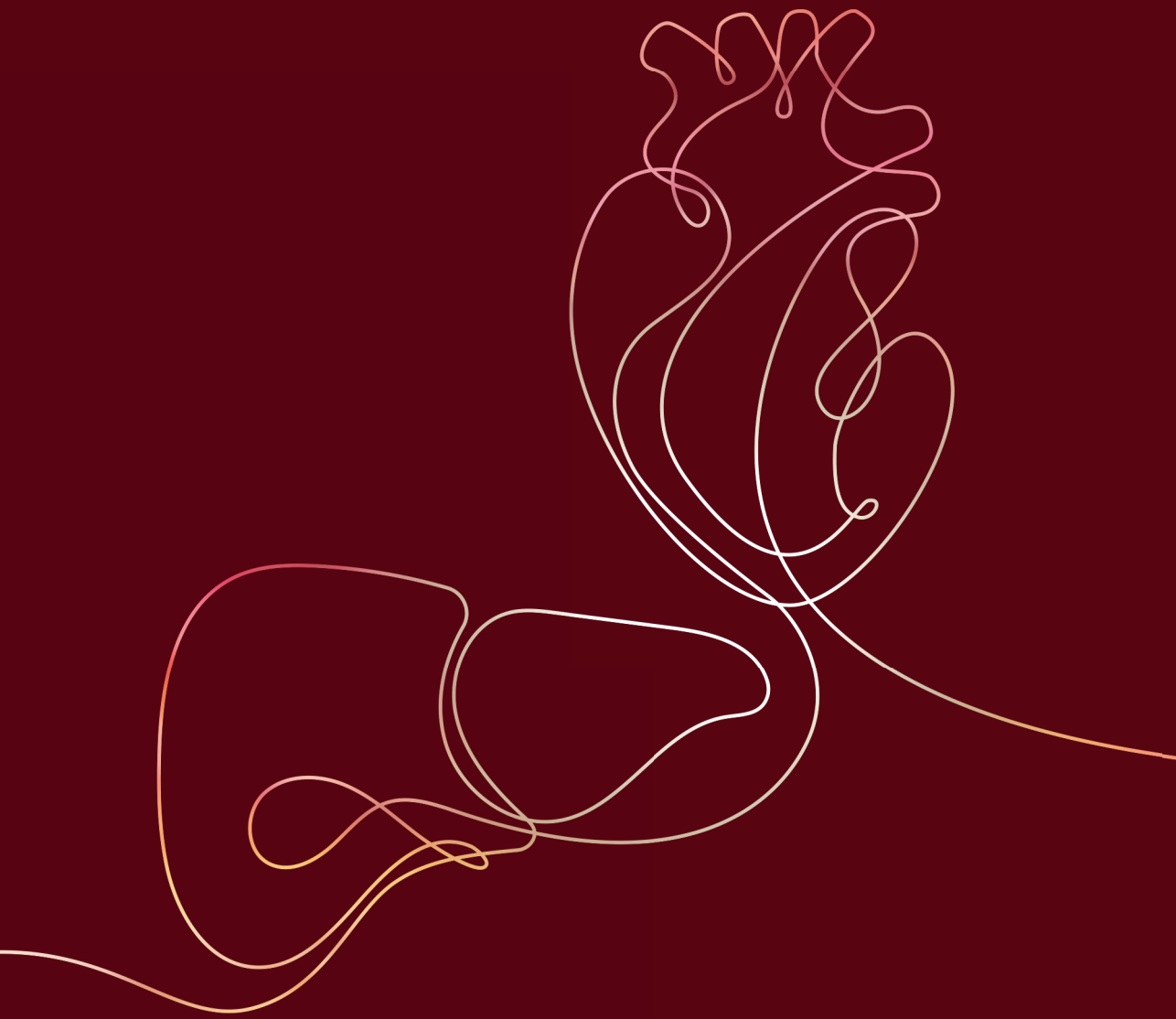

APPENDICES

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Summary

Metabolic syndrome affects an estimated 1.5 billion people worldwide, roughly one in five. Metabolic syndrome consists of a group of connected health problems including obesity and hypertension, dyslipidemia, and hyperglycemia, often resulting from long-term exposure to an unhealthy diet, physical inactivity and underlying conditions like type 2 diabetes. Implementation of lifestyle changes is the first approach in improving metabolic health. However, achieving and maintaining these changes can be difficult. When lifestyle changes are not enough, pharmacological interventions can provide an effective alternative to support weight management and reduce the risk of serious complications. In this thesis, several strategies were explored to better understand and reduce metabolic complications. Specifically, we investigated: (I) how repeated cycles of weight loss and regain affected metabolic health; (II) whether we can predict efficacy of treatments for liver disease; and (III) how both existing and experimental medications might improve metabolic outcomes. These studies were conducted in mouse models that closely mimic human metabolic processes.

In **Chapter 2**, we investigated the effects of repeated weight cycling, also known as yo-yo dieting. This repeated pattern of losing and regaining weight is often considered harmful, but is difficult to study in a controlled manner in humans. In this study, obese mice were exposed to alternating periods of healthy chow and a high fat diet. Surprisingly, we found that repeated weight cycling did not worsen health parameters compared to a continuous high fat diet. Instead, repeated weight cycling actually reduced hepatic inflammation, suggesting that even brief periods of healthy eating can yield lasting benefits.

In **Chapter 3**, we investigated whether early changes in gene expression can predict the efficacy of treatments targeting hepatic fibrosis. By examining fibrosis-associated genes shortly after treatment initiation, we found that early transcriptional signatures were reliable predictors of long-term therapeutic efficacy. This approach may help accelerate drug development by identifying promising compounds at an early stage.

In **Chapter 4**, we investigated bFKB1, and experimental FGF21-mimicking antibody. Despite eating more, obese mice treated with bFKB1 lost weight, displayed healthier adipose tissue, and showed improved glucose regulation. bFKB1 also reduced hepatic steatosis and inflammation, accompanied by improvements in vascular health. These findings indicate that targeting FGF21 signaling may provide a multifaceted therapeutic strategy for metabolic dysfunction.

In recent years, GLP-1 analogues like semaglutide that were originally developed to treat diabetes have become widely recognized for their strong effects on weight loss. However, their effects on the liver were not fully understood. Therefore in **Chapter 5**, obese mice with advanced MASLD were treated with semaglutide, which reduced liver steatosis and inflammation but did not improve fibrosis. Nevertheless, the structure of the hepatic collagen network was substantially improved by semaglutide. These findings suggest that semaglutide could be a promising treatment for improving liver health in people with MASLD, especially when combined with other therapies for more advanced liver damage

Despite the benefits of semaglutide, concerns have been raised regarding the long-term metabolic effects, particularly the loss of muscle mass. Preserving muscle mass during weight loss is essential to mitigate the risk of sarcopenia. In **Chapter 6**, we found that combining semaglutide with exercise helped reduce the loss of muscle mass and strength associated with semaglutide-induced weight loss. Together, these findings indicate that semaglutide has strong potential to improve liver health and reduce metabolic risk factors, while combination with exercise is essential to preserve muscle mass.

The cholesterol-lowering drug atorvastatin has been used for decades to prevent heart disease and to treat patients with dyslipidemia. We evaluated the effects of atorvastatin on MASLD in **Chapter 7** and found that on top of improving dyslipidemia, it decreased hepatic steatosis, inflammation, and fibrosis. These benefits were linked to prevention of harmful cholesterol crystal formation and inhibition of key inflammatory pathways. These findings indicate that statins are not only valuable for preventing and treating cardiovascular disease, but for improving liver health as well.

PCSK9 is an enzyme that raises cholesterol levels, thereby contributing to the development of heart disease. In **Chapter 8**, we tested a new peptide designed to block PCSK9. This peptide was tested both on its own and in combination with the ANGPTL3 inhibitor evinacumab. The peptide reduced cholesterol levels and helped reduce and stabilize atherosclerotic plaques. When combined with evinacumab, these effects were even stronger, leading to healthier vasculature with less inflammation and more stable plaque. These results further support the potential of PCSK9 inhibition, especially when combined with evinacumab, for treating atherosclerosis.

The CETP inhibitor obicetrapib is currently being tested in clinical trials for patients with high cholesterol and elevated cardiovascular risk. Although it strongly reduces cholesterol levels, the exact mechanism of action had not yet been elucidated. In **Chapter 9**, we evaluated the mechanism of action of obicetrapib in combination

with ezetimibe. Together, obicetrapib and ezetimibe enhanced the ability of the liver to clear cholesterol from the circulation by increasing the number of hepatic LDL receptors. This effect not only helped prevent the formation of new plaques but even reduced the size of existing plaques when asses to atorvastatin background therapy.

In conclusion, this thesis explores several promising strategies to reduce metabolic complications, with particular emphasis on liver and cardiovascular health. By integrating findings across weight-cycling physiology, early treatment-response gene expression changes, and multiple therapeutic targets, we show that metabolic dysfunction is best addressed through coordinated, multi-organ interventions rather than isolated pathways. Collectively, these studies deepen our understanding of metabolic disease biology and provide mechanistic support for more holistic, combination-based treatment approaches. These insights pave the way for more integrated treatments that address the complex nature of metabolic dysfunction.