Body composition, nutritional status and clinical outcomes in end-stage liver disease

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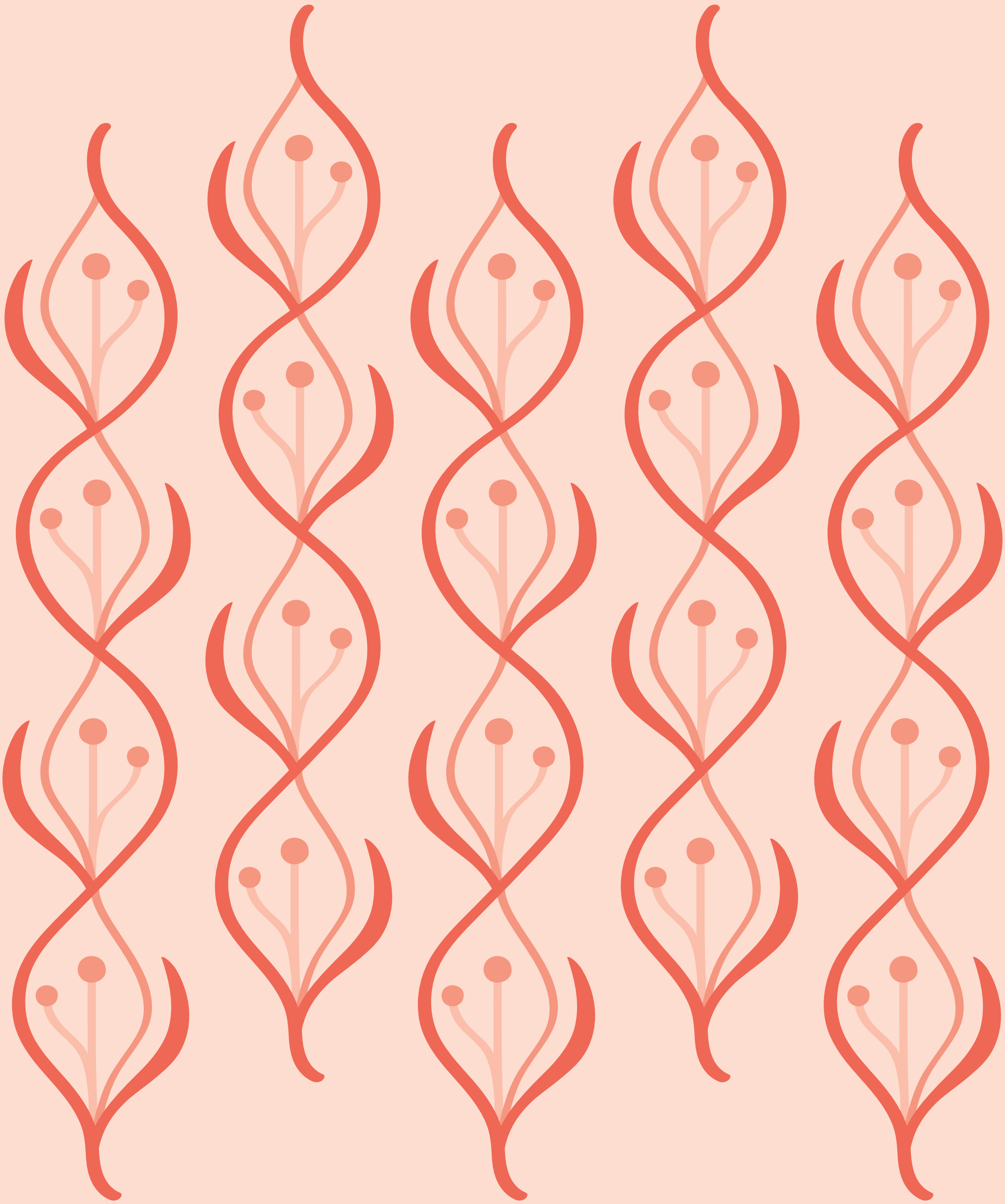

PART VI

THESIS OVERVIEW

10

Chapter 10

Summary, general discussion and future perspectives

Summary

In this thesis, an important aim was to better understand the relationship between body composition - in particular skeletal muscle index and muscle attenuation radiation -, nutritional status and clinical outcomes in patients with end-stage chronic liver disease. Alterations in body composition, such as sarcopenia (e.g. low skeletal muscle mass), myosteatosis (e.g. low skeletal muscle density) and sarcopenic obesity (presence of both sarcopenia and obesity BMI>30 kg/m^2) might occur during the disease course and may impact the clinical course.

In *chapter 2*, we retrospectively studied 261 patients waiting for liver transplantation between 2007 and 2014 at the LUMC. We used computed tomography (CT) scans to analyze individual body composition during the screening for waiting list placement. To assess the nutritional intake, we used data from dietary consultation at that time. In this chapter, we showed that both skeletal muscle index (SMI) and skeletal muscle radiation attenuation were associated with increased risk for mortality in patients with end-stage liver disease waiting for liver transplantation. SMI within the first quartile, reflecting the lowest SMI, was found to be a significant predictor of mortality on the liver transplant waiting list, with a hazard ratio of 2.580 (95%C.I. 1.06-6.31, P=0.04). The lowest quartile of muscle radiation attenuation had a statistically significant relation to mortality with a hazard ratio of 9.12 (95%C.I. 2.87-28.97, P<0.01). Energy and protein intake at time of waiting list placement were not associated with waiting list mortality risk in our cohort. These results show that patients with poor body composition at the moment of screening for liver transplantation, represented as the lowest quartiles of SMI and skeletal muscle radiation attenuation, have a higher risk to die during the waiting list period as compared to patients with higher levels of muscle mass or muscle quality.

Chapter 3 looks into the association of pre-transplant SMI and skeletal muscle radiation attenuation with post-transplant complications within the same cohort. Both SMI and muscle radiation attenuation were associated with post-liver transplantation outcomes. Cox regression showed a statistically significant association of muscle radiation attenuation with the one-year mortality rate (HR=0.656, 95% C.I. 0.464–0.921, P = 0.015). This HR shows that the hazard of one-year post-transplant mortality rate was reduced with 34% in patients with five-unit higher muscle radiation attenuation when adjusted for age, sex, and MELD-score. In the univariate analyses muscle radiation attenuation was associated with a higher 1-year post-transplant mortality rate and intensive care unit (ICU) stay (OR=0.273, 95% C.I. 0.105–0.708, P = 0.008); however, this was not confirmed in the multivariate analysis. Skeletal muscle index was associated with length of hospital stay >3 weeks in the multivariate analysis when adjusted for age, sex, and MELD score (OR=0.211, 95% C.I. 0.061–0.733, P = 0.014). The OR implies that the odds for a total length of stay in the hospital >3 weeks is 21.1 times lower in participants in the highest quartile of SMI compared with participants in the lowest category of skeletal muscle index. Early identification of patients with poor body composition is necessary and may limit the risk of post-transplant complications and mortality: These patients may benefit from more dietary or physical interventions to improve body

composition during the waiting list period.

In *chapter 4*, we studied the relationship between body composition and physical fitness in patients awaiting liver transplantation. This study was performed because changes in muscle tissue (for example myosteatosis) might result in reduced muscle function and decreased functional performance. It is known that muscle function and strength, reflected by gait speed and handgrip strength, are associated with dropping out of the waiting list for liver transplantation due to a declining health status. In this retrospective cohort study, we studied 152 patients waiting for liver transplantation. We observed their physical fitness with handgrip strength measurements and 6-minute walking distance (6MWD) measured by an experienced and trained physical therapist. We found that patients with myosteatosis (e.g. too low skeletal muscle radiation attenuation) had a lower walking distance (as percentage of predicted) compared to patients with normal muscle radiation attenuation. The odds for having a 6MWD <250m were significantly higher in patients with myosteatosis compared to the patients without myosteatosis. Low SMI was not associated with decreased cardiorespiratory fitness. Furthermore, presence of myosteatosis and/or low SMI were both not associated with general skeletal muscle strength, reflected by the handgrip strength. It can be concluded that assessment of myosteatosis, reflecting muscle quality, may help identifying patients who are at risk for the development of low cardiorespiratory fitness and can guide interventions during the waiting period for liver transplantation. Based on the high prevalence of myosteatosis in patients waiting for liver transplantation and on our findings, physical exercise training might be especially beneficial for patients with myosteatosis.

In *chapter 5*, the current accessibility and implementation of nutritional assessment to analyze individual patients' body composition in patients with chronic liver disease was studied. All dieticians who participated in this study had at least one nutritional assessment tool available to measure a patient's body composition. Imaging techniques were in most cases available in hospital settings, but many dieticians outside hospitals do not have easy access to these methods for analyzing body composition. We demonstrated that especially bio-electrical impedance analysis was available for patients with chronic liver disease and used for clinical care. The importance of measuring body composition is well-known to dieticians, and most hepatologists also acknowledge its importance for diagnosing nutritional status and for assessing risk of mortality. The most reported barriers for using nutritional assessment tools were lack of experience and evidence, high purchase costs and the time it consumes. Both the European Society of Parenteral and Enteral Nutrition (ESPEN) and the European Association for the Study of the Liver (EASL) have published recommendations regarding measurement of body composition in patients with liver diseases. Only about half of the participants -dieticians (49%) and hepatologists (60%)- were familiar with the 'ESPEN Guideline Clinical Nutrition in Liver disease' regarding the use of nutritional assessment. Of the dieticians, only 12.5% knew the 'EASL Clinical Practice Guidelines on nutrition in chronic liver disease' regarding the use of nutritional assessment and 60% of the hepatologists knew these guidelines. Even if the guidelines were known, they were not followed in many centers. It is clear from the results that, despite the fact that the importance of measuring body composition is reasonably known by dieticians and hepatologists and at least one nutritional assessment tool is available in almost all cases, implementation is lacking. Despite some knowledge regarding international guidelines regarding nutritional assessment in CLD, further education is also warranted.

In *chapter 6* and *chapter 7*, we demonstrate the clinical relevance of measuring resting energy expenditure in patients with end-stage liver disease. In *chapter 6*, we show in a small cohort of 29 patients with liver cirrhosis that there is a large clinically relevant difference between measured and calculated resting metabolic rate. The mean difference (± SD) in resting metabolic rate between measuring (Fitmate ©) and calculation (Harris and Benedict Equation) was 140 (± 240) kilocalories, with a minimum of -424 and a maximum of 510 kilocalories difference. For reliable dietary advice in patients with end-stage liver cirrhosis, resting energy expenditure should be measured with one of the newer easy-to-use devices, and should no longer be estimated with Harris and Benedict and other equations. This can have potential beneficial effects on nutritional status and therefore frailty in patients with liver diseases. In *chapter 7* we extended our research into this area of interest by investigating the association between energy balance (difference between energy intake and energy expenditure), late evening snack intake and body composition. We demonstrated that males with end-stage liver disease who had a negative energy balance had on average a lower skeletal muscle index as compared with males with a positive energy balance. A negative energy balance was found in 78.9% of the male patients (mean difference -548 ± 680 kcal/day) and 90% of the females (mean difference -443 ± 514 kcal/day). This energy difference corresponded to the mean amount of calories consumed in lunch or dinner in our study population. Also, more awareness regarding the advice for an optimal late evening snack should be considered. A higher SMI was found in males consuming an optimal late evening snack, containing 30g of carbohydrates and 15g of protein, compared to males who did not consume such snacks.

In *chapter 8*, we provide a systematic review of possible strategies to improve body composition in patients with end-stage liver disease. In this systematic review, nutrition, exercise, testosterone replacements and transjugular intrahepatic portosystemic shunt were found to be associated with improved muscle mass. Possible effective nutrition interventions were branched-chain amino acids supplementation, β-Hydroxy-β-methylbutyrate supplementation and a controlled diet with protein enriched oral supplement and dietetic counselling.

The potential effects of semaglutide on body composition in the treatment of Post-Transplant Diabetes Mellitus was reported in *chapter 9*. In a small cohort of ten patients with Post-Transplant Diabetes Mellitus following liver transplantation, we observed a significant decrease in body weight (111 ± 3 to 101 ± 2 kg, P<0.05) and HbA1c (66.1 (32.2-20.2) to 48.0 (28.7-58.8) mmol/mol (P<0.05) after six months of semaglutide treatment (0.5 mg once per week). BMI and waist circumference decreased significantly, from 34.9 ± 1.2 to 31.1 ± 0.8 kg/m^2 (P<0.05) and from 123.2 ± 3.3 to 100.7 ± 2.5 cm (P<0.05), respectively. There were no differences in trough levels and AUC0-3h of tacrolimus found. Mechanistically, semaglutide may even prevent tacrolimus-induced beta-cell failure by counteracting the activation of the BMP/SMAD signaling pathways. These findings need to be confirmed in larger studies with longer follow-up time.

General discussion

In the final part of this chapter, we will reflect on the main findings of our studies in this thesis. The findings will be interpreted in the broader context of care optimalization and personalized treatment. Furthermore, the contribution of the new insights into and suggestions for future research and implementation will be outlined.

In patients with liver disease, body composition, particularly muscle mass, plays an important role. Several muscle abnormalities can appear during the disease course of patients with liver disease resulting in poor body composition. Sarcopenia and myosteatosis are known to be unfavorable body composition types that are present in approximately 40% and over 50% of the patients with end-stage liver disease respectively. (1-3) Sarcopenia and myosteatosis are manifestations of a type of malnutrition characterized by low skeletal muscle mass (sarcopenia) and low skeletal muscle density due to infiltration of adipose tissue in the muscle mass, resulting in a lower quality type of muscle (myosteatosis). Sarcopenia is more prevalent in male patients and the prevalence is increasing with severity of the disease. (1) The findings in this thesis show that poor body composition is associated with lower physical fitness and higher mortality risk during the waiting list period for liver transplantation, and that it is associated with prolonged hospital stay and higher one-year mortality rate after liver transplantation *(chapter 2, 3 and 4)*.

The definition of malnutrition according to the European Society for Clinical Nutrition and Metabolism (ESPEN) is "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease". (4) The assessment of body composition is thus necessary to properly identify malnutrition. (5) Using reliable nutritional assessment tools to evaluate body composition is critical for clinical care and individual treatment of malnutrition and for improving body composition. The most available tools *(chapter 5)* in clinical care are double indirect measurement tools as bio-electrical impedance and traditional anthropometrics, meaning that the measurement is based on an indirect method with additional (statistical) assumptions. (6) Double indirect methods have considerable disadvantages in their reliability as -for example- high interobserver differences (circumference measures and skinfold thickness) or validity (bio-electrical impedance). (6, 7)

Current guidelines prescribe a standard assessment of sarcopenia, but there is still work to do for implementation in regular care *(chapter 5)*. This is surprising since scientific evidence to the relevance of sarcopenia has been increasing over the last decades. In most working area's in the Netherlands, at least one nutritional assessment tool is available for clinical practice. Most dieticians and hepatologists have at least hand-grip strength and bio-electrical impedance available at their center. As mentioned earlier, these methods are double indirect methods. At this point, bio-electrical impedance is highly influenced by fluid disbalances and therefore not reliable for the use in patients with (decompensated) liver diseases. The reference methods for assessment of body composition are indirect methods as the imaging techniques CT, magnetic resonance imaging (MRI) and dual-energy X-ray absorptiometry (DEXA). Imaging techniques are commonly used in medical diagnostics. Nowadays, only abdominal CT scans are used for determination of body composition in clinical care. This analysis is done by trained researchers or dieticians and is therefore time-consuming and expensive with limited availability. There are some automatic programs available, but they still have limitations and inaccuracies. The arrival of artificial intelligence and deep learning may make it possible in the future to do standard body composition determination on a larger scale in clinical practice. (8, 9) The general availability of imaging scans for body composition analysis is essential to gain insight into body composition of larger groups of patients. Standard assessment of body composition with every radiologic measurement that patients with chronic liver disease receive would help to gain more insight into changes over time and would allow for early diagnosis of abnormal body composition such as sarcopenia and myosteatosis. If imaging scans are not available, double indirect methods such as bioelectrical impedance could be used as an alternative, but the results of these measurements should be interpreted with caution.

Sarcopenic obesity is characterized by low skeletal muscle mass and obesity (BMI>30 kg/m^2) and is considered a more severe condition than sarcopenia or obesity alone. (10) The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) is over 30% worldwide and still increasing. As a consequence, MASLD has become a leading cause for liver transplantation in the Western World. (5, 11) In this particular etiology of end-stage liver disease, overweight and obesity are very common and sarcopenia often coexists. Alertness within this patient group for the presence of sarcopenia is important, especially given the results of our study described in *chapter 7* where we found that, besides a high body mass index, a negative energy balance was found in approximately two-third of the patients screened for liver transplantation. Although theoretically a negative energy balance could allow for weight loss and improvement in BMI in general, we see in patients with end-stage liver disease that a negative energy balance is associated with lower skeletal muscle mass. (12) Following the studies included in the systematic review *(chapter 8)* in this thesis, there is still a need for evidence based interventions in which weight loss can be achieved while preserving skeletal muscle mass. (13) Only a recent pilot study of Dunn et al., was performed targeting both muscle mass as well as adipose tissue. Even though they aimed to reduce body weight and fat mass while preserving muscle mass in patients with liver cirrhosis (alcoholic liver disease excluded), the loss of fat-free mass after a weight loss intervention with low calorie diet or alternate-day modified fasting, was quite high: respectively 34±20% (low-calorie diet) and 38±10% (alternate-day fasting) of the total weight loss occurred within 24-weeks. All patients within this study received advice on how to obtain sufficient protein intake, minimize protein catabolism during overnight fast by taking a late night snack and they participated in exercise classes, which are all described as possible interventions to improve sarcopenia *(chapter 8)*. (14)

The impact of myosteatosis in patients with liver disease is not yet as well known as the impact of sarcopenia. Regular assessment of myosteatosis has not been prescribed in international guidelines yet, but as we have shown in this thesis, the quality of muscle mass is relevant for physical fitness and related to one-year mortality after liver transplantation. In myosteatosis, the density of muscle mass is reduced due to infiltration of intramuscular fat into the muscle mass. Especially in patients with chronic disease and obesity, the prevalence of myosteatosis is higher. (15, 16) Interventions to increase muscle density have been very limited and have not been studied in patients with liver disease. There is some evidence that physical exercise might have a beneficial influence on muscle density in a healthy population. (17) The generalizability of these results to the population of patients with chronic liver disease may be limited given the study by Dunn. et al., in which it was shown that the proportion of muscle mass loss at start of intervention was relatively high in patients with liver disease. More research is this field is needed, with a focus on end-stage liver disease, aiming to improve muscle density in patients with liver disease without muscle mass breakdown. (14)

We showed that in end-stage liver disease measuring the resting energy expenditure is more reliable than calculating it, and that measurements should be preferred over equations to calculate energy expenditure in these patients for routine dietetic practice *(chapter 6 and 7)*. The mean-level agreement between the calculated and measured resting energy expenditure was good, but large individual differences, represented by a broad standard deviation, between the measured and calculated energy expenditures, makes the equations not reliable for setting the right personal nutritional targets in nutritional care. Providing an appropriate energy prescription is essential for effective nutritional therapy. Both hyper- and hypometabolism occurs in patients with liver cirrhosis. (18, 19) In many nutritional studies, information about the nutritional goal and the achievement of these goals are lacking. Besides, nutritional targets are set by equations with a high risk of over- and underestimation of nutritional needs, making it harder to provide clear conclusions regarding nutritional status of these patients. In a study of Chapman et al., hypermetabolism (measured resting energy expenditure (REE) >20% higher than calculated REE) was found in patients with more advanced liver disease (reflected by a higher MELD score). Such patients can have refractory ascites, and more often are severely malnourished. A possible disease specific equation for patients with liver disease to predict resting energy expenditure was presented in that study, but validation in larger cohorts should be performed prior to implementation in clinical care. Also, changes in energy requirements over time, for example due to disease progression or response to nutritional therapy, cannot be captured with predictive equations. (20) This means that there are enough reasons to implement indirect calorimetry measurement in all patients with severe liver disease, as is already mentioned in international guidelines. A current problem is that indirect calorimetry is a relatively expensive tool which is not available in all healthcare settings. However, collaboration between hospitals and healthcare settings in which patients with liver disease are measured at least once at diagnosis and preferably also in case of major changes during the disease process or at standard intervals, would be a solution to address the problem of availability. Besides, recently a more affordable indirect calorimeter has become available on the market, which may enable the purchase of an indirect calorimeter by more care centers.

The studies from this thesis provide a scientific basis for the evidence-based use of nutritional assessment measurements in routine clinical practice in liver disease. We have demonstrated the consequences of unfavorable body composition and provide guidance on interventions in clinical care. Malnutrition with unfavorable body composition, both sarcopenia and myosteatosis, is a serious complication of liver disease with potentially major consequences for the patient in terms of mortality and morbidity. At the same time, it is potentially treatable and thus interventions can have major clinical impact.

Methodological considerations

In the studies in this thesis, we used CT scans as method to assess body composition. This method is very reliable and recommended by international guidelines of ESPEN and EASL to assess body composition in patients with end-stage liver disease. Body composition assessment in patients with end-stage liver disease is influenced by fluid imbalances. One of the complications of liver cirrhosis is the presence of ascites. Extensive screening for liver transplantation by a dietician is part of usual care in transplant centers. Wider implementation in non-transplant centers should be stimulated as part of standard clinical data collection. Performing nutritional research with randomized clinical trials is challenging due to the nature of these studies. For example, the challenge of blinding participants, high daily variations in nutritional intake or food patterns and personal nutritional needs makes it difficult to design such studies and make clear conclusions. Studies into additional supplementations or enteral nutrition have on average a lower risk of bias compared to studies into dietary intake with regular foods. Methods that can be used to track dietary intake have the disadvantage that they can be inaccurate. Based on previous studies, underreporting of dietary intake is known to occur especially in overweight people and overreporting in underweight people. In addition, recall bias may occur because participants may not fully remember their dietary intake. To reduce this risk of bias, we used data collected by experienced and registered dietitians with reference equipment in the studies conducted within this thesis.

Future directions

- Assessment of body composition in an early state during the disease course, with regular follow-up, should be implemented in standard clinical care.
- Prevention of sarcopenia and myosteatosis should play a more important role in care for patients with liver diseases.
- Treatment of sarcopenia and myosteatosis should become part of the care pathway, given their negative associations with waiting list mortality, one-year mortality after liver

transplantation, complications and physical fitness.

- The presence of sarcopenia or low skeletal muscle index, analyzed with reliable measurement tools as imaging techniques (CT scans), should be taken into consideration when deciding to list a patient for liver transplant.
- In almost every setting at least one nutritional assessment tool is available to access the body composition. Standard use of these methods should be implemented to identify patients with poor body composition.
- Cooperation between healthcare centers and out-of-hospital dieticians, regarding use of body composition assessment methods could solve the problem of insufficient availability of reliable methods for measuring body composition and resting energy expenditure.
- Development of care pathways, in which nutritional care plays an important role early after diagnosis and during follow-up, even if no nutritional-related complaints occur, may improve outcome.
- With the increased prevalence of overweight and obesity in society, alertness to sarcopenia, sarcopenic obesity and myosteatosis is needed.
- Longitudinal studies are needed to determine at which points during the disease process deterioration of body composition occurs.
- High quality homogeneous intervention studies, in the field of lifestyle and nutrition, with sufficient participants, reliable measurement tools and enough follow-up time are needed.
- Research on patient-reported outcomes and patients experiences and perceptions in relation to their body composition and malnutrition should be performed.

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