PART I

INTRODUCTION

1

Chapter 1

General introduction and outline of the thesis

Introduction

Liver cirrhosis is caused by chronic inflammation, cholestasis or metabolic disorders and is the result of fibrogenesis and regeneration (Figure 1). The result is a shrunken, nodular liver that can no longer perform its functions properly due to cirrhotic complications that develop as the disease progresses. End-stage liver disease (ESLD), including liver cirrhosis, is a major health burden. In 2023, worldwide, approximately two million deaths per year are caused by liver disease. (1) In the Netherlands, the prevalence of liver cirrhosis is estimated at 75.2 patients per 100.000 in 2021. (2) The etiology of liver cirrhosis can be alcohol, metabolic (in most cases related to lifestyle), viral, cholestatic or auto-immune. At the final stage of chronic liver disease, a liver transplantation is the only curative treatment. Liver transplantation is the second most common solid organ transplant worldwide. (1) In the Netherlands, liver transplantations are performed in three academic medical centers including the Leiden University Medical Center. Since 2006, allocation of livers for transplantation has been based on the Model For End-stage Liver Disease (MELD) score. This score predicts the chance of surviving the next three months. (3-4) The MELD score is calculated from blood levels of the International Normalized Ratio (INR), creatinine, bilirubin, and ranges from 6 till 40 points. In time, improvements have been made by adding other parameters including sodium -for the MELD-Na score- serum, and sex and serum albumin for MELD 3.0. (5) In general, patients with original MELD scores below 15 are not listed for liver transplantation, since the gain in survival does not outweigh transplantation risks (including perioperative complications). In the Netherlands, in recent years most patients were on the waiting list for 0-5 months, followed by a quarter of the patients waiting for 6 to 11 months. (6) During this period, disease progression and complications may occur. Highly prevalent complications in ESLD are ascites, hepatic encephalopathy, esophageal varices (that can bleed), infections (including spontaneous bacterial peritonitis) and hepatocellular carcinoma. In 2023, 259 patients were removed from the waiting list for liver transplantation in the Netherlands. The majority (207 patients, 80%) underwent transplantation. Twenty-five patients (9.7%) died and eight patients (3.1%) were considered unfit for transplantation. Twelve patients (4.6%) recovered without a transplant, and seven patients (2.7%) were removed for reasons other than those mentioned above. (6)

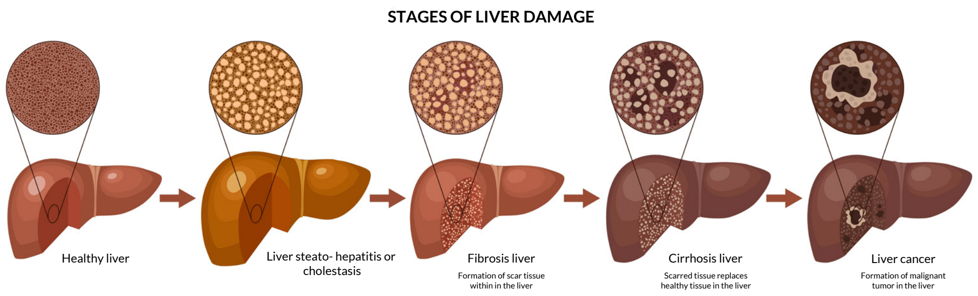

Figure 1. Stages of liver damage (source: shutterstock.com)

Malnutrition is frequently present in ESLD. It is prevalent in approximately 20% of patients with compensated and more than 50% of patients with decompensated liver cirrhosis. The prevalence of malnutrition is associated with the progression of the disease and may influence outcomes. (7) 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". (8) The published prevalence of malnutrition in patients with ESLD is highly influenced by the chosen definition, cut-off values and the diagnostic tool used. Many factors are influencing the nutritional status of a patient with ESLD. First, insufficient intake of nutrients by reduced oral intake can cause malnutrition. This can be due to anorexia, early satiety, nausea, ascites, fatigue, altered taste and smell and cognitive impairment due to hepatic encephalopathy. Secondly, maldigestion and malabsorption might occur due to reduced bile production, altered intestinal motility, portal hypertensive gastropathy or enteropathy and the use of lactulose. Third, changes in metabolism are an important factor, especially in patients with cirrhotic liver disease: increased gluconeogenesis, insulin resistance, decreased glycogen synthesis and storage, and the early use of protein and lipids for energy production and glucogenesis are affecting the metabolism. (9) It has been observed that fat and protein catabolism after a short overnight fast in patients with liver cirrhosis is similar to that of healthy individuals who underwent two or three days of starvation. (10)

Malnutrition leads to altered body composition, in particular decreased fat free mass and body cell mass. Only body weight or body mass index (BMI) does not provide sufficient information; the proportion of adipose tissue and muscle tissue should be measured to gain insight into a patient's body composition, as recommended in the guidelines of the European Society of Parenteral and Enteral Nutrition (ESPEN) and the European Association for the Study of the Liver (EASL). (7, 11, 12) Body composition can be analysed using direct, indirect or double-indirect methods. The more indirect the measurement, the lower the reliability. (13) Direct methods are labelled water, total body counting and neutron activation and -after death- with cadaver analysis. (14) Indirect methods are dual-X-ray absorptiometry (DEXA), densitometry, magnetic resonance imaging (MRI) and computed tomography (CT). (11, 12) Double indirect methods are bio-electrical impedance analysis (BIA), and traditional anthropometrics such as skinfold thickness and circumference measurements. The indirect methods are based on a simplified version of the human body via compartmental models (Figure 2) and the results of these methods are based on various statistical assumptions. (15, 16) Indirect methods, such as radiologic measurements, are based on multi-compartment models. Double indirect methods are mostly based on the basic 2 or 3 compartment models. (15, 17)

Basic 2- Compartment Model	Basic 3-Compartment Model	Basic 4-Compartment Model	5/Multi Compartment Model
Fat Mass (FM) Adipose tissue and fat)	**Fat Mass (FM)** Adipose tissue and fat)	**Fat Mass (FM)** Adipose tissue and fat)	Level 5: Whole body
Fat-Free Mass (FFM) (Carbohydrates, Protein, Water, Minerals)	**Water**	**Fat-Free Mass (FFM)** Body cell mass	Level 4: Tissue
			Level 3: Cellular
	Fat-Free Mass (FFM) (Carbohydrates, Protein, Water, Minerals)	Extracellular water (ECW)	Level 2: Moleculair
		Extracellular Solid (ECS)	Level 1: Atomic

Figure 2. Compartment models for analysis of body composition

Optimising body composition and nutritional status is a complex process involving various factors. Examples of alterations in body composition include sarcopenia (e.g. low skeletal muscle mass) and myosteatosis (e.g. low skeletal muscle density), obesity (e.g. body mass index ≥25 kg/m^2) and sarcopenic obesity (presence of both sarcopenia and obesity). (18) Although in particular muscle mass is well studied, muscle density and adiposity seem to play important roles as well. The risks associated with (sarcopenic) obesity are driven by specific adipose tissue compartments. (19) Adipose tissue can be divided in subcutaneous, intramuscular or visceral compartments. Visceral adipose tissue, which surrounds the intra-abdominal organs, is negatively influencing different hormonal and immunologic pathways. Next to sarcopenia, myosteatosis (e.g. low skeletal muscle quality reflected by low skeletal muscle density) seems to be associated with several clinical outcomes. (18) Although the recognition of the importance of body composition and nutritional status in patients with ESLD is rising, still many important questions remain, like those regarding association with clinical outcomes including patient reported outcomes, implementation in usual care and therapeutic approaches. These are the topics of this thesis.

Outline of this thesis

This thesis focusses on the importance of body composition and nutritional status in patients with ESLD. After this introduction, the second part of this thesis describes the impact of body composition and nutritional intake on several outcomes before and after liver transplantation in patients with ESLD. In *chapter 2* the consequences of poor body composition, especially skeletal muscle mass, for outcome during the waiting list period for liver transplantation were investigated. In *chapter 3* the impact of low skeletal muscle index and muscle radiation attenuation on mortality and several complications during the first year after liver transplantation was investigated. In *chapter 4* the topic of investigation was the association between skeletal muscle index and skeletal muscle radiation attenuation on the one hand, and physical fitness on the other hand in patients with ESLD. In the third part in *chapter 5*, we report on the current availability and use of nutritional assessment tools by dieticians and hepatologists to assess the individual body composition of patients with liver disease in clinical care. The fourth section of this thesis is focusing on determining the patients energy needs. *Chapter 6* describes the challenges in assessing nutritional needs and shows the importance of measuring the resting metabolic rate in patients with liver cirrhosis. *Chapter 7* discusses the relationship between energy balance, late evening snack intake, energy expenditure and body composition in patients screened for liver transplantation. The fifth part of this thesis is mainly focusing on interventions to improve body composition in patients with ESLD throughout the course of their disease. In *chapter 8* we present a systematic review on the possible strategies to improve body composition in patients with end-stage liver disease. *Chapter 9* describes the effects of semaglutide injections on obese patients with post liver transplant diabetes mellitus in a small case series. Finally, *chapter 10* summarises and discusses the main findings of this thesis in light of the current literature and considers the possibilities for future research and implementation in clinical care.

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