Malnutrition in end stage liver disease

Who is malnourished?

Ellen J. Huisman

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Ondervoeding bij het eindstadium van leverziekten

Wie is ondervoed?
(met samenvatting in het Nederlands)

Proefschrift

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Chapter 1

General introduction

End stage liver disease, or liver cirrhosis (**Figure 1**), is a significant cause of global health burden, with 1.2 million deaths worldwide in 2013 (1). The prevalence of liver disease in general is estimated at approximately 450 million people worldwide.

Figure 1. In end stage liver disease scar tissue replaces the healthy hepatocytes, blocking normal function and blood flow (source: IStock).

Major causes of liver disease and cirrhosis are heavy alcohol use (384,000 deaths in 2013) and viral infections such as hepatitis B or C (317,000 versus 358,000 deaths in 2013) worldwide (1). Other causes are autoimmune or hereditary diseases, non-alcoholic fatty liver disease or chronic cholestatic diseases. Roughly 29 million people in the European Union suffer from a chronic liver disease (EASL 2013). Liver disease is becoming even more relevant in recent years as comparative mortality rates for various diseases in the United Kingdom during the last decades illustrate. Large health resources have been invested in other areas (e.g., cardiac disease), decreasing mortality substantially. Liver disease is the exception (**Figure 2**) (2).

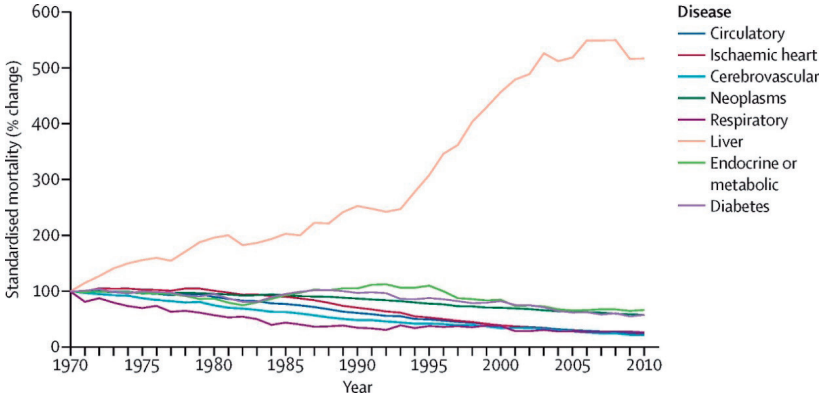

Figure 2. Comparative mortality rates in the United Kingdom (2)

Liver diseases in general may lead to an inflammatory state, regardless underlying cause. Liver disease most often progresses slowly from (depending on underlying cause) inflammation to progressive fibrosis (deposition of excess extracellular matrix, rich in fibril-forming collagens). At the late stages of this process, cirrhosis will have developed in some cases as a common end point, regardless underlying aetiology. Normal functions of the liver become progressively compromised due to the formation of scar tissue. **Figure 3**. shows the different stages of a hepatitis C infection. Even in late stages of liver disease the damage caused by this inflammation can be (partly) reversible, although reversibility declines as liver disease advances (3).

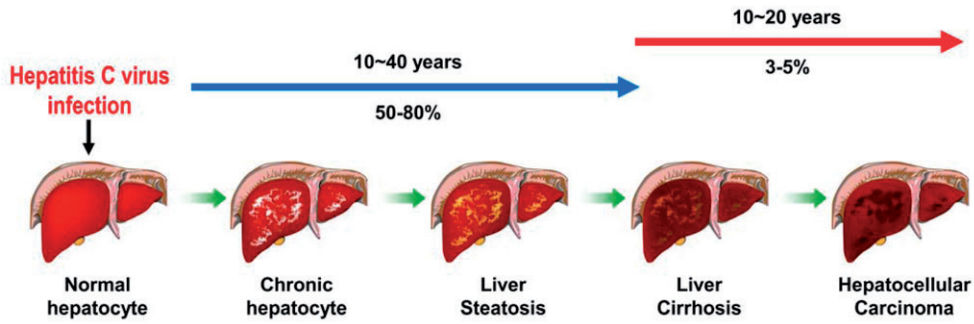

Figure 3. Various stages of liver disease; liver steatosis, fibrosis and cirrhosis (4). Reprinted with permission of author and publisher.

Liver disease disrupts many physiological and biochemical processes of the liver including the metabolism of carbohydrates, protein and fat. It alters dietary intake and leads to malabsorption and maldigestion of nutrients (5-7). This phenomenon leads to many problems, including the development of malnutrition which is highly prevalent in patients with liver cirrhosis. This is quite relevant as different types of malnutrition may enhance liver disease and even are, in some cases, potential risk factors for the development of liver disease.

It has not yet been established whether adequate nutrition can prevent cirrhosis or even decrease the risk of progressive liver disease. Nevertheless, we do know that what we eat greatly affects the human body. In health, after entering the blood stream, the type and amount of carbohydrates we consume have major implications on the time in which its breakdown products are released as glucose into the blood. This is defined as the glycaemic load (GL). Carbohydrates with a high GL will quickly fill glycogen storages and, when these storages are full or inaccessible, excess glucose will be stored in fat cells. Carbohydrates with a low GL release glucose molecules more slowly, providing a more stable supply of energy and reduce storage as fat (8). The type of fat we ingest, defined by the length of its chains of triglycerides, not only determines how quickly its fatty acids will become available in the blood. This also influences the amount of blood flowing toward the intestine to transport

these fatty acids (and other nutrients) to the liver and beyond. Long chain triglycerides provide the largest increase in blood flow. Supplementing long chain triglycerides with pancreatic enzymes (and thus increasing the digestion into fatty acids), increases this blood flow even more (9). Excess fatty acids are stored in adipose tissue. The type of carbohydrate as well as fat therefore influence metabolism directly. The amount and quality of the protein we eat also affect functioning of our organs, skin, muscles, immune system, enzymes, hormones and even neurotransmitters. These are only a few examples to illustrate the importance of nutrition, even at the level of macronutrients, in general.

In disease, optimal nutrition becomes even more important. Consideration of nutrition in liver disease is especially relevant as virtually all portal blood, with nutrients absorbed from the intestine, will normally pass through the liver. In the liver, these nutrients are converted, stored or both. In cirrhosis, the liver is often less capable of performing all the unique and essential metabolic tasks to store or convert these nutrients into substances the body can use. Simply due to loss of healthy hepatocytes with formation of scar tissue (fibrous septa), the storage of glucose as glycogen (needed when no energy is taken in) is heavily compromised. The diseased liver also loses much of its unique ability to convert amino acids into glucose when needed. Both processes render patients with cirrhosis susceptible to hypoglycemia, muscle breakdown and immune-compromised state. Proteins will generally have been digested in the intestinal lumen into amino acids or converted to toxic ammonia before reaching the liver. In health, the liver breaks down the ammonia into urea which is then excreted by the kidneys. The amino acids can either be used as building blocks for proteins (Including muscle mass), used as source of energy by the muscle, stored for later use or, like ammonia, converted into urea. In cirrhosis, these processes can be compromised, leading to depletion of energy, muscle mass and, sometimes, hepatic encephalopathy. Also, the digestion and absorption of fat and fat soluble vitamins can be decreased and deficiencies in various micronutrients frequently occur.

In **Chapter 2**, we review the prevalence of malnutrition in cirrhosis, the effect of liver disease on nutrient metabolism, maldigestion, and malabsorbtion and the effect of the nutritional status on the liver. In this chapter, also some advises are given to tailor current dietary guidelines to cirrhotic patients. Whether malnutrition is relevant in Dutch patients with cirrhosis is explored in a large cohort in **Chapter 3**.

The effect of nutrition on the human body starts directly after intake, before uptake in the blood stream. For example, the type and amount of carbohydrates we ingest, has considerable effects on the composition of our intestinal bacteria. Eating the right carbohydrates (prebiotic fibres) will enhance growth of lactobacilli, bifidobacteria, Akkermansia and butyrate-producing bacteria in the intestine, with potentially beneficial effects on health state (10). Intestinal bacteria digest our food, affect the immune system, synthesize vitamins and ensure the barrier function of the gut wall. They provide a large portion of the energy needed by our gut mucosal tissue (11). As the integrity of the intestinal wall may be compromised in case of liver disease, promoting a healthy intestinal flora via

the intake of the right foods becomes even more relevant (12, 13). In **Chapter 4,** potential effects of proton pump inhibitors, on the intestinal integrity are explored in complementary animal and human studies.

The hepatitis C virus (HCV) is the one of the major causes of liver disease. The World Health Organisation estimates that there are more than 170 chronic carriers of HCV worldwide. In 10-20% of cases, the infection may progress to liver cirrhosis after 20 years follow up (WHO 2015 Global alert and response). PEG-interferon-containing antiviral treatment for hepatitis C is reasonably effective but is associated with severe side effects, including rapid weight loss and digestive symptoms leading to a malnourished state. Combining carbohydrates with a low glycaemic load with protein may not only stabilize blood glucose levels, but may also enhance muscle preservation. As muscle atrophy is a major disorder in malnutrition (particularly in liver disease), this simple approach could be important. Adding a little fat to this mixture could in addition, retards the passage of food from the stomach to the small intestine, possibly providing the human body with more gradual supply of energy and building blocks for cell membranes and hormones. In **Chapter 5** potential beneficial effects of the above mentioned combinations of macronutrients in the diet on the nutritional state during antiviral treatment for hepatitis C are examined in a randomized controlled trial. In 2015, hepatitis C is not treated with PEG interferon but with all oral direct acting antivirals. Nevertheless, our study should be regarded as “proof of principle” that dietary interventions can have substantial beneficial effects on patient health and quality of life during very demanding therapies. Labour productivity and physical activity are also strongly reduced in patients receiving PEG-Interferon containing antiviral treatment for hepatitis C. In **Chapter 6** the effect of preventive nutritional advice and support on paid labour productivity and the ability to stay physically active during this treatment is described. In **Chapter 7**, we provide a summary and some concluding remarks.

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Chapter 2

Malnutrition in end stage liver disease: Is it time to differentiate the diagnostics?

Ellen J. Huisman

Departments of Gastroenterology and Hepatology,
University Medical Centre Utrecht, The Netherlands.

To be published

Abstract

Protein energy malnutrition, which is strongly associated with higher morbidity and mortality, is highly prevalent in patients with end stage liver disease. However, the term protein energy malnutrition includes two types of malnutrition; protein malnutrition and true protein energy malnutrition with both calorie and protein deficiency, but this does not differentiate between these two. In addition, it also emphasises on deficiency and excludes a scarcely recognised type of malnutrition, i.e. (severe) overweight in its many forms. Nonetheless, these latter types present a serious health risk, especially in patients with end stage liver disease. The prognosis of patients with (severe) overweight is therefore poor and the prognosis of patients with (severe) overweight in combination with other types of malnutrition is even poorer and less recognised. Current clinically used diagnostic tools cannot identify these patients accurately nor do current nutritional guidelines acknowledge (severe) overweight or (severe) overweight in combination with protein malnutrition properly. Here we aim to give an overview of malnutrition in patients with end stage liver disease based on a differentiation in the definition of malnutrition, dissecting protein energy malnutrition into true protein energy malnutrition, protein malnutrition, (severe) overweight and combinations of the latter two.

Introduction

The prevalence of malnutrition is high in patients with end stage liver disease, i.e. liver cirrhosis. The most commonly reported type of malnutrition in these patients is protein energy malnutrition (PEM), defined as a deficit in both protein and energy or a deficit in protein with sufficient energy (WHO, 1993). Major contributing factors to malnutrition are an inadequate dietary intake, malabsorption and maldigestion of both macro- and micronutrients, and hypermetabolism (1-4). PEM, well described elsewhere, is strongly associated with a deterioration of liver function (5), development of complications (5, 6), lower quality of life (7) and a higher morbidity and mortality (8-11). The term PEM does not differentiate between a deficit in both protein and energy or a deficit in protein with sufficient energy. Furthermore, it excludes at least one major type of malnutrition, namely (severe) overweight ((S)O) in itself a known risk factor for the development of cirrhosis (12).

(S)O is barely recognised as a type of malnutrition in the clinical setting and only recently has become a topic of interest in research in cirrhotics. Our studies, however, have shown that the prevalence of (S)O is extremely high (45%) in Dutch cirrhotic patients (13). We found no depletion or only sufficiency of energy in these patients. Moreover, protein malnutrition (PM) was diagnosed in up to 67% of these (S)O patients. This indicates that these patients actually suffer from two types of malnutrition; (S)O and PM, which has its specific health risks (14). Furthermore, contours of a new type of (S)O are rising, i.e. the existence of an excess of fat mass (>25% in men, >30% in women) in individuals without overweight according to body mass index (BMI); normal weight obesity (NWO) (15-18). NWO patients have low or even insufficient muscle mass. Whether NWO is present in patients with liver cirrhosis can, for now, only be deducted from data on protein deficiency and body weight or body fat mass. Our research has shown that the prevalence of underweight (BMI ≤ 18.5), indicating both energy and protein malnutrition, here defined as true PEM (tPEM), was merely 5% in cirrhotics in the Netherlands (13). Apart from macronutrient deficiencies but beyond the scope of this chapter, patients with liver cirrhosis often develop micronutrient deficiencies. All these distinct types of malnutrition have specific serious implications for health in general. Combinations of types of malnutrition pose an even bigger health risk. In end stage liver disease these factors may increase the severity of disease and induce a specific type of liver disease, non-alcoholic fatty liver disease (NAFLD).

Despite their importance, all types of malnutrition, even those broadly termed PEM, are clinically underdiagnosed in cirrhotic patients (19, 20). Particularly in the late stages of disease (21) malnutrition is often masked by fluid retention (22). Markers for protein deficiency are not yet used in a clinical setting and (S)O or NWO are rarely recognized as types of malnutrition at all. Fortunately, there are now studies available on PM in combination with obesity in these patients. Here we aim to review current literature on the prevalence, prognosis, aetiology and pathophysiology of PM, (S)O or NWO with or without PM in patients with liver cirrhosis worldwide.

Methods

A systemic literature search was conducted using Pubmed for 'end stage liver disease', or 'liver cirrhosis' in combination with 'nutrition', 'body composition', 'malnutrition', 'sarcopenia', 'cachexia', 'obesity', 'weight', 'muscle mass'. Only studies from January 2000 until December 2015, giving information on BMI, protein and or fat mass, were evaluated as earlier data may not reflect the current status of malnutrition due to the significant increase in prevalence of overweight, obesity and NWO in the general population (12). As many types of malnutrition are not recognised as such in literature, we propose a differentiation in the definition of malnutrition based on BMI, muscle mass sufficiency and percentage of body fat (**Table 1**). Even though micronutrient malnutrition falls beyond the scope of this review, we do include it here (as well as some examples later) to emphasis its importance in patients with liver cirrhosis. We used this differentiation to be able to at least give an indication of the prevalence of all types of malnutrition.

Table 1. Types of malnutrition

	Muscle mass	Percentage of body fat**	Micronutrient deficiencies
Protein energy malnutrition (PEM)			
True protein energy malnutrition (tPEM)	Insufficient	Insufficient	Yes
Protein malnutrition (PM)	Insufficient	Sufficient	Yes/No
Underweight*	Sufficient	Insufficient	Yes/No
Normal weight* with excess fat mass (NWO)			
Normal weight* with overweight	Sufficient or low	High	Yes/No
Normal weight* obesity (NWO with PM)	Insufficient	Extremely high	Yes/No
(Severe) overweight* (S)O	Sufficient	(Extremely) high	Yes/No
(Severe) overweight* with protein deficiency	Insufficient	(Extremely) high	Yes/No
Micronutrient malnutrition (MM)	Sufficient	Sufficient	Yes

*Weight according to the BMI
**Percentage of body fat (23):

- Insufficient (♀ < 14%, ♂ < 8%)
- Sufficient (♀ ≥ 14% - < 25% , ♂ ≥ 8% - < 18%)
- High (♀ ≥ 25% - 35%, ♂ ≥ 18% - 25%)
- (Extremely) high (♀ > 25%, ♂ > 18%)
- Extremely high (♀ ≥ 35%, ♂ ≥ 25%)(23)

Epidemiology

In this section an overview of the epidemiology of all different types of malnutrition in patients with end stage liver disease is presented. **Table 2** provides an overview of the prevalences of the different types of malnutrition in patients with liver cirrhosis.

True protein energy malnutrition (TPEM)

As there is no gold standard for the diagnosis all types of malnutrition in patients with end stage liver disease, different parameters or combinations of these, are used. This explains the large range of prevalences of malnutrition in cirrhotics. PEM has been reported in 5-75% of patients with compensated cirrhosis and in 46-94% of patients with decompensated cirrhosis (13, 24-26) and is independent of the aetiology of liver disease. PEM is diagnosed in up to 100% of patients on the waiting list for liver transplantation (LT) (27). Studies have also indicated that the prevalence of PEM is already high (up to 34%) in patients with early stage cirrhosis (28, 29). We found that tPEM, with both protein and energy deficiency, was rarely reported. When mentioned, or deductible from data, its prevalence appeared to be very low (1%-8%) and generally is mostly seen in patients with Child Pugh C cirrhosis (13, 30, 31).

(Severe) overweight (S)O, including normal weight obesity (NWO)

The standard parameter for (S)O, the BMI, is not useful in patients with decompensated liver cirrhosis as fluid retention may cause an overestimation of body weight. It is also not accurate in patients without fluid retention, or even in healthy individuals, due to the possibility of NWO. Myosteatosis, or infiltration of fat into skeletal muscle, complicates this even further. Therefore, little is known about the prevalence of (S)O in patients with liver cirrhosis. In the data we collected, the percentage of (S)O ranges from 22% up to 61% (6, 13, 15, 30, 32). Figuerido *et al.* published data on standard BMI indicating that body weight reduced and total body water increased in patients with Child Pugh class C cirrhosis (33). The average BMI in Child Pugh class A and B (with no significant fluid retention) however was high, 27 ± 5.1 and 26 ± 4.4, respectively, indicating substantial overweight (even without taking NWO into account) in these classes. The BMI corrected for estimated fluid retention (BMIc) can be used as an alternative, as it shows a strong correlation between estimated and measured dry weight, according to Richards *et al.* (34, 35). Of the 45% of Dutch patients with liver cirrhosis and S(O) according to this parameter, we found that 25% was overweight (BMIc ≥ 25-29.5), 14% obese (BMI ≥ 30-34.9), 5% severely obese (BMI ≥ 35-39.5) and 1% morbid obese (BMI ≥ 40). These prevalences were independent of Child Pugh class (13). Everhart *et al.* reported that more than 75% of patients included in the HALT-C trial (study on the effect of maintenance PEG interferon for advanced hepatitis C) were overweight (BMI ≥ 25) and 44% of them were obese (BMI ≥ 30). Of these patients, 45% had compensated cirrhosis, whereas the remainder had a histologic diagnosis of bridging fibrosis, the last stage before cirrhosis occurs (33). Additionally, moderate to severe obesity was shown

to be present in up to 32% of liver transplant candidates (36). These percentages were independent of disease aetiology, except for cryptogenic cirrhosis. Cryptogenic cirrhosis accounts for an increasing proportion of liver transplants in the Western world and is often caused by unrecognized NAFLD (37). The prevalence of NWO in patients with liver cirrhosis has only been reported by Tandon *et al.*, with 46% of normal weight patients having cachexia (38) and in our research (60%) (13). It is also known that NASH frequently occurs in normal weight patients (39). Possibly, these patients have NWO.

Protein malnutrition (PM) and PM with (severe) overweight (S)O

In other studies more expensive and time consuming methods to evaluate body composition, including fat mass have been used. The emphasis here was however mostly on protein deficiency, which is recognized as a major risk factor in patients with liver cirrhosis. In a large study, Peng *et al.* reported protein deficiency in 51% of all patients, which significantly increased with increasing Child Pugh class. Protein deficiency was already present in 40% of patients with Child Pugh class A cirrhosis. In this study both absolute fat mass and total body fat as percentage of total body mass was not different between Child Pugh classes (40). In fact, the average percentage of total body fat indicated obesity in men with Child Pugh class A cirrhosis and overweight in men with Child Pugh class B and C cirrhosis. The average of total body fat percentage in women of all Child Pugh classes was extremely high. This indicates that PM together with S(O) is highly prevalent in these patients. The prevalence of protein deficiency, with or without a high body fat mass, can also be derived from data on lean body mass as measured by the body cell mass and parameters of muscle strength. Figueiredo *et al.* found protein depletion in 51% of cirrhotic patients using hand grip strength. Also, 40% of patients with Child Pugh class A cirrhosis was already protein depleted (41). We found hand grip strength insufficiency, indicating PM, in 67% of Dutch patients with liver cirrhosis. These percentages were 60% and 71% in patients with normal weight and PM or (S)O with PM, respectively (13).

Examples of micronutrient malnutrition (MM)

The prevalence of MM is also high in cirrhotic patients. For example, vitamin D deficiency has been shown to be present in two thirds of patients with liver cirrhosis and 96% of patients awaiting liver transplantation (42). Water-soluble vitamin deficiencies have also been found. Low concentrations of vitamin B6 have been reported in 35% of patients with cirrhosis. Available studies show a high risk of mineral deficiencies like calcium (43), magnesium, copper and phosphate deficiencies (44, 45). There is not enough information to make assumptions on the exact prevalences of the different MM's in combination with other types of malnutrition in cirrhotics.

Prognosis

There is much information on the prognosis of PEM in liver disease (49, 50). Information on the prognosis of the more specific types and combinations of types of malnutrition other than PEM, such as (S)O, PM and NWO with or without PM in end stage liver diseases is however rare.

Severe obesity ((S)O)

Obesity, in itself, is associated with an increased risk of mortality (51), type 2 diabetes (52), cardiovascular diseases and cancer (53). More specifically, obese individuals without cirrhosis have a 7 times higher risk of developing diabetes than individuals with normal BMI (54). These, and other disorders such as inflammation, metabolic syndrome, non-alcoholic fatty liver disease associated with (S)O, have a major impact on general and liver health. In patients already suffering from liver disease, (S)O poses even higher risks as all grades of overweight are risk factors for the development of cirrhosis in viral, alcoholic, and non-alcoholic fatty liver disease (55-57). (S)O-associated inflammation, insulin resistance and excess free fatty acids affect the liver and therefore the progression of cirrhosis in general. The increased risk of developing cirrhosis with obesity (compared to normal or low BMI) was estimated to be 30%-50% (12). A high BMI value was found to be a risk factor for the development of hepatocellular carcinoma (HCC), especially in men. Hyperinsulinemia, associated with a high BMI and prevalent in cirrhotics, has also been shown to be a risk factor for HCC (58)(46).

Table 2. Prevalence of malnutrition in end stage liver disease

Malnutrition	Compensated cirrhosis	Decompensated cirrhosis
Protein energy malnutrition (PEM)	5 – 75.3% (28, 29)	46 – 94% (13, 24-26)
True protein energy malnutrition (tPEM)		1 – 8% CP C only (13, 30, 31)
(Severe) Overweight ((S)O)	22 – 61% in all, but higher in CP C (6, 13, 15, 30, 32)	
Normal weight obesity (NWO)	46 – 60% of all CP classes (13, 38)	
Protein malnutrition (PM)	40 - 43% (13, 46)	Up to 51% (13, 40, 47)
Protein malnutrition (PM) & normal weight obesity (NWO)	Up to 60% of all CP classes (13)	
Protein malnutrition (PM) & (severe) overweight ((S)O)	Up to 71% of all CP classes (13, 46)	
Micronutrient malnutrition (MM) (examples)	Up to 67% of all CP classes (vitamin D) (42) Up to 35% of all CP classes (B vitamins) (48)	

Of note: these prevalences do overlap due to the lack of proper markers for the different types of malnutrition

Excess body fat is associated with the accumulation of fat in the liver. In the United States, recent studies suggest that non-alcoholic fatty liver disease (NAFLD) affects 30% of the general population and is as high as 90% of individuals that are morbidly obese. The available data indicate a prevalence rate of NAFLD up to 44% in the general population of Europe (59). Of note, Braverman *et al.* classified 39% of outpatients of a multispecialty private practice in the United States as NWO (18)(47). NALFD in turn can lead to non-alcoholic steatohepatitis (NASH), which is estimated to occur in as many as 40% of patients who have elevated liver enzymes in the setting of negative serologic markers for a viral or auto-immune cause and hemochromatosis (60). NASH is associated with an increased risk of progression of fibrosis and complications such as HCC. Also, (S)O and insulin resistance are independent risk factors for NASH (61), which is considered to be the major cause of cryptogenic cirrhosis (62). Cirrhosis develops in 15-25% of patients with NASH and up to 40% of these cirrhotic patients eventually die from a liver disease-related cause over a 10-year period (63, 64).

An analysis of the data of 73,538 adult liver transplants in the US has shown that severely obese patients (≥ 40 kg/m^2) had significantly lower survival rates and a higher number of infectious complications and cancer events leading to death (65). Many physicians believe that obesity (≥ 30 kg/m^2) is a significant risk factor for complications and death after liver transplantation. This is based on the clinical impression that a surgical procedure in obese patients is more complicated and is associated with an increased peri-operative morbidity compared to non-obese patients. Many obese patients are therefore placed under dietary restrictions. PEM is, however, often diagnosed in these same patients, indicating protein deficiency. Standard dietary restrictions may therefore be detrimental to these patients.

Protein malnutrition (PM)

Recent studies have reported on the detrimental effects of PM in patients with liver cirrhosis. Hanai *et al.*, among many others, found that cachexia, diagnosed by computed tomography (CT), is significantly associated with mortality in these patients (66). This was found to be independent of the severity of liver disease (67, 68). In cirrhotics with HCC, cachexia (diagnosed with CT) is a strong and independent risk factor for mortality (69). Muscle function, as assessed by hand grip strength, was reported to be closely related to total body protein and even more to protein loss (70). A reduced midlife hand grip strength has been associated with long term mortality in general (56). In patients with liver cirrhosis, hand grip strength on admission to the hospital was shown to be a predictor of outcome after one year of follow-up (71, 72). We found that PM as diagnosed by hand grip strength is an independent predictor of complications in outpatients with liver cirrhosis (13).

Protein malnutrition (PM) and severe obesity ((S)O)

PM in combination with (S)O does not influence liver size (73) but is associated with a higher mortality in cirrothics according to Montano-Loza *et al.* (46). They found that cirrothic

patients with a combination of PM, obesity and myosteatosis had the lowest probability of survival after six months of follow-up (**Figure 1**)(68).

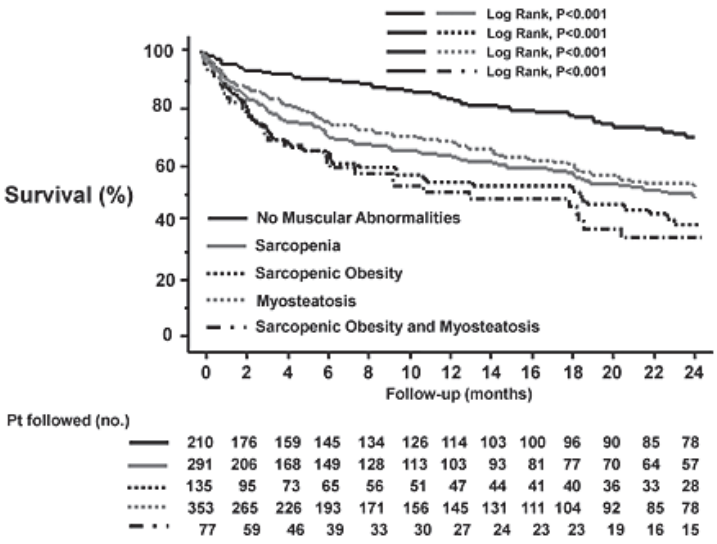

Figure 1. Effects of various forms of malnutrition on survival in cirrhotics (46). Reprinted with permission from author and publisher.

Aetiology

The aetiology of malnutrition in cirrhosis is multifactorial and often develops in the early stage of disease (74), irrespective of the aetiology of the liver disease (75). Liver disease disrupts the many physiological and biochemical processes of the liver including the metabolism of carbohydrates, protein and fat, which can lead to various problems, including the development of malnutrition. Other major contributing factors leading to PEM are an inadequate dietary intake (13, 40), malabsorption and -digestion of both macro- and micronutrients (76-78), and abnormal substrate utilization including hypermetabolism (79-81) A reduced synthesis and increased loss of protein specifically contribute to the pathogenesis of PEM, severely impairing health (70, 82-88). All have been described elsewhere in detail. Here we focus on those aetiologies leading to (S)O, PM or a combination thereof.

Overconsumption

The high prevalence of (S)O in patients with liver cirrhosis indicates overconsumption in these patients. General and disease-related inactivity is likely to contribute to this phenomenon as

well (89), leading to severe loss of muscle mass and insulin resistance. The total body muscle mass uses up to 50% of total energy consumption during exercise but also 20% in rest. Inactivity decreases energy expenditure and the loss of muscle mass and insulin resistance related to inactivity decreases energy expenditure even further. Overconsumption of calories in general may therefore easily occur in patients with liver cirrhosis. Furthermore, food choices are influenced by chronic stress, which is frequently high (90) as quality of life is often low in patients with liver cirrhosis (91)(8;40;74). Chronic stress increases the motivation to eat more fat- and carbohydrate-rich food, especially those foods with a high glycaemic load (92), thereby increasing insulin secretion and free fatty acids. These changes in food preference are independent of hyperphagia or hypohagia (**Figure 2**) (77).

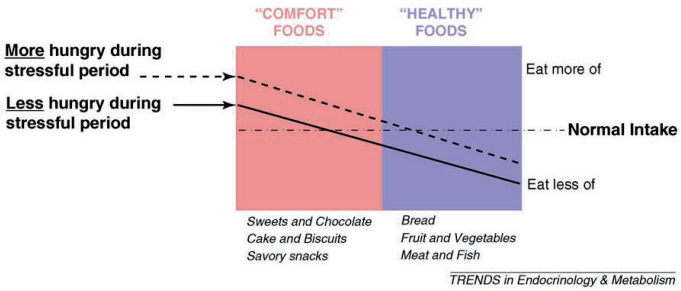

Figure 2. During stressful periods, there is a shift in food intake toward 'comfort foods' that is independent of whether total caloric intake increases (dashed line) or decreases (unbroken line) from normal intake (horizontal dot–dashed line) (93). Reprinted with permission from author and publisher.

Glycogen storage capacity of the cirrhotic liver is diminished and insulin resistance of the myocyte often precedes insulin resistance elsewhere, reducing glycogen storage in the muscle. Carbohydrates are quickly digested into glucose and can only be stored as fat. Chronic stress may also increase insulin secretion, increasing this storage even further (89, 93). Consumption of specific vegetable oils (omega 6 rich bean and seed oils) and their derived products (e.g. margarines and baked foods) that coincides with an increase in 'comfort' foods lead to (S)O with free fatty acids and inflammation (94).

Even a low caloric diet with only a relative overconsumption of carbohydrates and fat can therefore induce fat storage, especially since restriction of calories increases the total output of cortisol, promoting further fat storage (78). Moreover, a low caloric diet is a stress factor, promoting craving for foods with a high glycaemic load or fat content. Patients with liver cirrhosis often state they do not tolerate high fat products or fear that the intake of too much fat may cause liver damage. These patients may therefore be even more likely to choose highly glycaemic foods. Few studies have been conducted on changes in the proportion of macronutrients in the diet of these patients. Recently, we found that protein intake was significantly deceased with increasing Child-Pugh classes. We also found a shift

from protein to carbohydrate as reflected by increasing ratio carbohydrate/protein intake (in energy percentage, En%) with increasing severity of liver disease. This ratio was also significantly higher in patients with as compared to patients without malnutrition (13).

Undernutrition

The negative effects of insufficient intake of vitamins, minerals and other bioactive substances on patients with liver disease has been described elsewhere in detail. Dietary fibre however deserves mentioning here as their intake is extremely low in the general population (insufficient in 95% of Dutch adult population, Nationaal Kompas). Intake of specific dietary fibre from non-starchy vegetables is even lower. These specific fibres normally feed healthy microbiota in the gut. If not available, healthy microbiotica wither and make room for less favourable bacteria, leading to immune dysregulation, inducing and enhancing inflammation already present in cirrhosis (95). Gut-derived toxins, such as lipopolysaccharides, have been implicated as cofactors of liver injury, including NASH (80, 96), hepatic encephalopathy and HCC (97). As colonocytes derive up to 70% of their energy from short chain fatty acids produced by healthy microbiota, insufficient dietary fibre may lead to deterioration of these cells and their tight junctions, which may increase gut permeability (98). As disturbances of gut microbiota are highly prevalent in patients with liver disease (97), this is relevant in these patients.

Muscle protein loss

Inactivity, in general and disease related, is already enough to significantly reduce muscle mass. In patients with liver disease this is combined with disease related tissue breakdown. An extreme type of hypermetabolism, which may occur in up to 50% of cirrhotics, is cachexia (40). Cachexia is defined as a complex metabolic syndrome characterized by anorexia, accelerated skeletal muscle protein breakdown and enhanced branched-chain fatty acid oxidation causing muscle wasting with or without loss of fat mass (99-101). It is associated with the underlying disease and occurs in acute inflammatory processes associated with critical illness and in chronic inflammatory diseases such as liver cirrhosis. The underlying mechanisms responsible for cachexia are related to pro-inflammatory cytokines, sympathetic nervous system activation and enhanced cortisol production followed by complex metabolic alterations, but are not completely understood (102, 103). Raised levels of endotoxins produced by an imbalanced gut, as is common in cirrhosis (2), and cachexia stimulating cytokine release do positively correlate with energy expenditure (80, 104-109). It can be the underlying cause of sarcopenia.

Furthermore, patients with liver cirrhosis have a greater metabolic response to short-term starvation. Studies have indicated that patients with liver cirrhosis have a marked decrease in glucose oxidation with enhanced fat and protein catabolism after an overnight fast, similar to that observed in healthy subjects after a 2- 3-day period of total starvation. This catabolic state could not be prevented with a normal breakfast the next morning (82,

110). A nocturnal nutritional supplement did however prevent a catabolic state in these patients and resulted in a protein accretion equivalent to about 2 kg of lean tissue sustained over a period of 12 months when compared to a control group not receiving nocturnal nutritional supplementation (111). This indicates that limiting the overnight fasting period with supplementation blunts early onset of nocturnal gluconeogenesis from amino acids, thereby improving nitrogen balance. These benefits were already seen in patients at the early stages of cirrhosis (Child Pugh A).

The early onset of gluconeogenesis from amino acids in fasting indicates that hepatic glycogen storage is extremely low in cirrhotics. Loss of hepatic storage of glycogen in these patients in combination with peripheral tissue insulin resistance was shown to reduce the energy efficiency of glucose from 96% to 41%. Additionally, glucagon resistance occurs and, consequently, the liver switches to gluconeogenesis from amino acids, mostly branched-chain amino acids. The oxidation of branched-chain amino acids therefore may compensatory rise and occurs especially in skeletal muscles (112). Hyperammonemia due to an impaired hepatic capacity to detoxicate ammonia is common in cirrhotics. Instead, skeletal muscles and, to a lesser extent the brain, clear blood ammonia by incorporating ammonia in the production of glutamine. The precursor of this process, glutamate, requires branched-chain amino acids for this production. The pronounced clearance of plasma branched-chain amino acids found in cirrhotics may at least partly be explained by the enhanced uptake and consumption of branched-chain amino acids by skeletal muscles for ammonia detoxification. Furthermore, several studies have also indicated that ammonia may have an inhibitory effect on protein syntheses (99). All these processes strongly promote PM.

Pathophysiology of malnutrition in liver cirrhosis

The pathophysiology of PEM has been reviewed in detail elsewhere (113-115). The pathophysiology of (S)O, PM or NWO with or without PM, in patients with liver cirrhosis is less well described. Below, a more in-depth description of the pathophysiology of these latter types in patients with liver cirrhosis is presented.

(Severe) overweight ((S)O) in cirrhosis

Obesity is associated with an increased risk of mortality (51), type 2 diabetes (52), cardiovascular diseases and cancer (53). The increased fat mass induces biochemical and physiological changes that affect the whole body, including the liver. It may aggravate the complications of any disease, including liver cirrhosis. Moreover, these changes may initiate cirrhosis itself by inducing NAFLD (116-121).

The expanded adipose tissue, whether peripheral of ectopic (e.g. in the liver), is chronically inflamed (122-124). Oxygen delivery to this tissue and the production of anti-inflammatory cytokines is decreased. This leads to local changes in gene-expression and eventually to cell death, already rampant in cirrhosis. Adipose tissue-resident immune cells release multiple pro-inflammatory cytokines, chemokines, adipokines that may block insulin action in adipose

tissue, muscle and the liver, thus promoting general insulin resistance. These substances are able to induce hepatic cholesterologenesis, thereby disrupting lipid metabolism, and stimulate collagen expression and the prevention of apoptosis of steatotic hepatocytes. This promotes hepatocellular injury and enhances existing liver disease (125).

The expanded adipose tissue also release free fatty acids into the circulation by activate inflammatory pathways impairing normal cell signalling within adipose tissue, immune and muscle cells, causing cellular dysfunction. In health, free fatty acids are transported from the liver and stored in peripheral fat stores. When this transport mechanism or the storage of fat becomes overwhelmed, triglycerides are retained in the liver (126), leading to non-alcoholic fatty liver disease (NAFLD) (60, 127). This occurs predominantly in Kupffer cells, directly initiating liver injury (125, 128). General accumulation of ceramides, a free fatty acid metabolite and pro-apoptotic lipid, leads to cell death ultimately contributing to cachexia and cirrhosis (129, 130). In muscle and liver tissue, the intracellular accumulation of fatty acid metabolites triggers the impairment of insulin signalling. The resulting high plasma glucose levels may induce further inflammation and is metabolised into even more triglycerides. Indeed, glucose itself has an inhibitory effect on liver regeneration (131). High plasma glucose levels induce high plasma insulin levels which decrease mobilization of fatty acid from the liver as a result of inhibition of hormone-sensitive lipase (99). Patients with cirrhosis are already hyperinsulinemic due to a reduced glycogen storage capacity of the liver and muscle promoting excessive free fatty acids (132). Hypoglycaemia in fasting is also a frequent event due to hyperinsulinemia when approximately 80% of hepatocytes are dysfunctional in cirrhosis. Hyperglycaemia, which can develop when these same patients are given glucose, acts as a stimulus of the secretion of profibrogenic cytokines (133). This may also be induced by a diet with a high glycaemic load associated with (S)O. Importantly, patients with liver cirrhosis have significant insulin resistance in the liver and skeletal muscle, but not in adipose tissue (14). This indicates that excess dietary glucose may not be used as an energy source for muscle tissue but is stored in adipose tissue, fat in muscle tissue (myosteatosis) or is directly metabolised into even more free fatty acids, even without (S)O, thereby instigating a vicious circle.

(S)O induced insulin resistance, hyperinsulinemia, relatively low levels of glucagon and an impaired response of the pancreas may be the pathophysiological bases of type 2, but also hepatogenous, diabetes mellitus (131, 134, 135). Indeed, up to 96% of patients with cirrhosis may be glucose intolerant and up to 25% of patients with cirrhosis have diabetes mellitus (DM) (133, 136, 137). Patients with cryptogenic liver cirrhosis, associated with excessive body fat mass, were found to have a significantly higher prevalence of both DM (47% respectively 22%) and obesity (55% versus 24%) than patients with cirrhosis from other aetiologies. Micronutrient deficiencies of vitamin D, E, C, folic acid and B vitamins, associated with insulin resistance, are also associated with both (S)O and liver cirrhosis (138-140).

Significantly elevated levels of oestradiol and oestrone and low levels of testosterone are often found in men with liver cirrhosis due to the inability of the liver to metabolize these hormones. These men develop gynecomastia, erythema palmare and spider angiomas and such levels are associated with adverse health outcomes, including the risk of breast cancer (141, 142). (S)O, in general, is characterized by relatively high levels of oestrogens since adipose tissue highly expresses P450 aromatase. Few studies have been done on the effect of the combination of overexpression and inability to metabolize oestrogens in (S)O cirrhotic men or women.

Of major importance is the difference between peripheral subcutaneous fat mass, associated with a low metabolic risk, and ectopic fat mass, associated with a high metabolic risk (143). Excessive subcutaneous fat may serve as a buffer (144). When subcutaneous storage of fat is impaired or overwhelmed, even with modest weight gain, excess fat will store in ectopic tissue (for example, the liver and pancreas). This ectopic fat leads to organ-specific insulin resistance, depressing its function (145). Ectopic lipid accumulation in liver and skeletal muscle both trigger pathways that impair insulin signalling, leading to reduced muscle glucose uptake and decreased hepatic glycogen synthesis. Muscle insulin resistance, due to ectopic lipids, precedes liver insulin resistance and diverts ingested glucose to the liver, resulting in even more ectopic fat accumulation in the liver. Cirrhotic patients with ectopic fat accumulation are therefore at an even higher risk of developing type 2 diabetes but also further deterioration of liver function

PM in cirrhosis

PM may be cachexic (disease related) or sacropenic (age related) or both. It also occurs in otherwise healthy individuals due to a lack of exercise and an inappropriate diet. The skeletal muscle mass is the largest component of the body responsible for the insulin-stimulated disposal of glucose, accounting for 85% of whole body insulin stimulated glucose uptake, and is therefore an important regulator of blood glucose homeostasis (147). The significant insulin resistance in skeletal muscle, as opposed to adipose tissue, may interfere with this regulatory function (14). Disturbances in muscle free fatty acid metabolism, caused by disturbances in cytokines, chemokines and adipokines associated with liver cirrhosis (see above) may also contribute to the development of impaired activation of insulin receptors in skeletal muscle (148). The impaired ability of glucose and free fatty acid oxidation in muscle tissue contributes to an increased oxidation of amino acids. If these are not available, endogenous amino acids may be used. The largest source of amino acids in the body is the skeletal muscle mass. Low levels of circulating amino acids from the diet therefore result in wasting of skeletal muscle and impaired synthesis of protein. More specifically, endogenous branched-chain amino acids from skeletal muscle may then be used as an energy substrate (149, 150).

Furthermore, a sufficient insulin response is needed to maintain muscle mass, whereas the effect of insulin on branched-chain amino acid metabolism is reduced in cirrhotics (149).

Muscle protein synthesis may only be stimulated with a combination of a low concentration of insulin (5-7 mU·L-1), adequate glucose levels (5.4 mM), and systemic amino acids infusion (141). A systemic infusion of insulin and energy without the infusion of amino acids does not increase muscle protein synthesis (151). Fujita et al. have also shown that hyperinsulinemia only stimulates an increase in muscle protein synthesis when accompanied by increased amino acids delivery. Amino acids are the primary factor driving maintenance of muscle mass by increasing muscle protein synthesis. Insulin or energy (glucose) alone can modulate the response but are not sufficient to support a full synthetic response (152). Indeed, a significant reduction of skeletal muscle protein synthesis in cirrhotic patients has been found by Morrison et al. (84, 153).

Other factors affecting skeletal muscle protein synthesis and regeneration of muscle satellite cells include insulin growth factor-1 (IGF-1) and myostatin and are respectively under- and overexpressed in cirrhotics. This may result in further skeletal muscle wasting (154). Disease related immobility, as mentioned earlier, also contributes to muscle mass loss. Stress, which is associated with chronic illness, increases plasma cortisol levels. It has been suggested that cortisol is one of the primary mediators of catabolism of muscle protein. A combination of prolonged immobility and chronically increased levels of cortisol was found to substantially increase muscle protein catabolism (155).

PM combined with (S)O in cirrhosis

In patients with PM and (S)O all the factors of both types of malnutrition are combined. Moreover, these factors enhance each other. The impaired glucose tolerance in cirrhosis was found to be due mainly to an impaired insulin reception in skeletal muscles while adipose tissue is still responsive to insulin (14). Muscle cell insulin resistance instead of fat cell insulin resistance in combination with hyperinsulinemia may therefore promote (severe) overweight, especially in cirrhotics with a high glycaemic load in the diet. Also, the oxidation of free fatty acids in skeletal muscle is reduced in patients with liver cirrhosis. This reduction of free fatty acid oxidation leads to accumulation of fat in the muscle and to adipose tissue expansion, thus adding to the vicious circle of loss of protein mass and an increase in fat mass. The accumulation of fat mass with a reduction of muscle mass augments (S)O but may also lead to NWO, especially as the fat mass is lighter in weight than the protein mass it replaces. Recent research showed that even in healthy individuals this shift is taking place (17, 18). McCullough *et al.* showed that this shift is however greater in patients with cirrhosis (27). Montano-Loza *et al.* found that the frequency of sepsis related death was significantly higher in cirrothics with PM in combination with obesity, confirming an even more immunocompromised state in these patients (46)

Diagnosis

In this paragraph, an overview of diagnostic tools of the nutritional status used in a clinical setting (**Table 3**) and a research setting (**Table 4**) in patients with liver cirrhosis is presented

with their strengths and limitations. We propose a combination of practical markers for early identification that may accurately assess protein and ectopic fat mass.

Diagnosis in the clinical setting

Currently used clinical diagnostic tools have major pitfalls (**Table 3**). They measure only one component and/or relay on assumptions that are not valid in a high percentage of cirrhotics or even in healthy subjects. The presence of ectopic fat is not measured at all.

For cirrhotics with fluid retention a marker for ectopic fat is urgently needed. With such marker (in combination with hand grip strength and BMIc), it may be possible to identify all types of macro malnutrition in the clinical setting in all cirrhotic patients (**Table 5**).

Table 3. Diagnostic tools in a clinical setting

Non useful tools	
BMI	Does not differentiate between fat and lean body mass, and does not correct for fluid retention (12,78). Reference values may no longer be valid due to the rise of NWO.
Triceps skin-fold thickness (TSF) and mid-arm muscle circumference (MAMC)	TSF does not assess protein mass. Both are corrupted by ectopic fat accumulation (myosteatosis), oedema and gender (179, 180, 181). Most reference date from 1981 (156).
Subjective global assessment adjusted for patients with liver cirrhosis (SGA)	Sensitive for 22% in patients with liver cirrhosis; underestimation in 57% (186). Based on BMI (see above).
Combination of the SGA with TSF, MAMC and an override based on the subjective opinion of the investigator	Does not identify the different types of malnutrition. All pitfalls of BMI, TSF and MAMC. The combination of these markers was significantly associated with mortality in cirrhotics (9, 157). Possibly due to the subjective (but correct) opinion of the investigator.
Useful tools	
Hand grip strength	Best and independent predictor of complications in patients with liver cirrhosis (13). Measures muscle strength and reflects a chronic detriment in general physical health rather than severity of liver disease (158). It is a risk-stratifying method for all-cause death, cardiovascular death, and cardiovascular disease in the general population (159). A sensitive and specific marker of body cell mass depletion in patients with liver cirrhosis (188). Associated with longer ICU stay and more postoperative infections (160). It is not biased by fluid retention or S(O). Amendable by nutritional intervention (4)
Without fluid retention Waist-to-hip circumference	Measure adiposity related risks (161) and independently associated with increased risk of NAFLD (162). Amendable by nutritional intervention
Without fluid retention Hand grip strength with BMI and waist-to-hip ratio	Best combination of markers to diagnose malnutrition in cirrhotic patients without fluid retention. HGS in combination with BMI and waist-to-hip ratio allows for the differentiation between NWO and PM (see **table 5**).
With fluid retention Hand grip strength with BMIc	For now the best combination of markers to diagnose malnutrition in cirrhotic patients with fluid retention. BMI corrected for fluid retention (BMIc) shows a strong correlation between estimated and measured dry weight (34, 35). Does need validation for outpatients. Waist-to-hip ratio needed to differentiation between NWO and PM cannot be used in these patients (see **table 5**).

Diagnosis in a research setting

Even the gold standard 4 component model, distinguishing between water, fat, protein and mineral mass, seems not to include a direct assessment of body protein. In this model, it is assumed that muscle mass contributes to at least 70% of the body cell mass (25, 28). This is most likely no longer a valid assumption, due to the high prevalence of ectopic fat and NWO. Most 2-or 3-component models also do not include a direct measurement of body protein either. They not only base body protein mass, but also water mass on the assumption that the constancy of the density and hydration fraction of fat-free mass which is violated in patients with liver cirrhosis and fluid retention and ectopic fat (46, 157) (**Table 4**).

Table 4. Diagnostic tools in a research setting.

Non useful tools	
Standard biochemical indicators of malnutrition	Common indicators of malnutrition, albumin and transthyretin, cannot be used in patients with liver cirrhosis as they are synthesized in the liver and therefore affected in liver disease.
Other biochemical indicators affected by liver disease	The concentration of branched-chain amino acids and aromatic amino acids, as well as the serum levels of certain cytokines, such as TNF-a, adiponectin (and leptin), are related to the degree of hepatic decompensation (5, 163-165).
Dual energy X-ray (DEXA)	Does not assess fat distribution and is based on assumptions of protein and fat ratios that may no longer be valid. Fluid retention invalidates DEXA (201).
Bioelectrical impedance analysis (BIA) and its phase angle	BIA assesses the body composition according to its resistance and its reactance to a small electrical current. Not accurate in patients with fluid retention (166). Does not assess fat distribution and the results are compared with specific healthy populations (167, 168) which may no longer be valid.
Vector–BIA; Vectorial analysis method, or resistance/reactance graph	Classifies the state of hydration and compares it with a normal population, adjusted for sex and race and uses a cut-off point to define malnutrition in cirrhotic patients (169). Not valid with fluid retention and based on assumptions on fat and protein mass which may no longer be valid. Does no assess fat distribution.
Other body cell mass calculations	Parameter of the metabolically active compartment of lean tissue are obtained with many different methods. All use assumptions that may no longer be valid and do not assess fat distribution.
Total body nitrogen	Measured by prompt gamma in vivo neutron activation analysis. Total body protein is then calculated as 6.25 times total body nitrogen which may no longer be valid (170). Results are compared with specific healthy populations (167, 168) which may no longer be valid.
4 component tool (body weight, densitometry, deuterium dilution, and DEXA): golden standard	Protein mass is based on assumptions that may no longer be valid.
Useful tools	
Muscularity and adiposity assessment with computer tomography (CT) scan or MRI	Identifies patients at risk (49, 199). Muscle wasting reflects a chronic detriment in general physical health rather than acute severity of liver disease and is not biased by fluid retention (158). Still, cut-off values are used that possible need revision.
Without fluid retention Hand grip strength with BMI and waist-to-hip ratio	Combination of markers to diagnose malnutrition in cirrhotic patients without fluid retention. BMI in combination with waist-to-hip ratio differentiation between NWO and PM (see **table 5**)

A proper combination of practical markers for early identification should accurately assess, not assume, protein mass and ectopic fat (**Table 5**). This combination should identify all malnourished patients, be positively influenced by nutritional intervention and this improvement should reduce risks. For now, hand grip strength, BMI and waist-to-hip ratio may provide such combination at least for cirrhotic patients without fluid retention. Combining hand grip strength and BMIc (after validation for outpatients) with a marker for ectopic body fat that is also an independent predictor of complications in cirrhotics, may provide the simple solution for an accurate diagnosis of malnutrition in cirrhotics with fluid retention. Markers of the metabolic syndrome or liver fat content could possibly be useful here. Combining these markers with a thorough assessment of dietary intake, including meal frequency, ratio of macronutrients and nutrient density (micronutrient assessment) may provide the best insight in the nutritional status of these patients and therefore their current and future health risks and need for nutritional support. Currently, scoring systems of the mortality risk of end stage liver disease (Child Pugh and MELD score) have limitations. Including a correct assessment of the nutritional status into these scoring systems (not included now) may increase their sensitivity and specificity, though further research is needed.

Table 5. Diagnosis of the nutritional status of patients with liver cirrhosis without and with fluid retention.

	Nutritional status of cirrhotics without fluid retention							
	Healthy	**tPEM**	**Underweight**	**PM**	**NWO**	**NWO & PM**	**(S)O**	**(S)O & PM**
BMI	Normal	Low	Low	Normal	Normal	Normal	High	High
HGS	Normal	Low	Normal	Insufficient	Sufficient	Insufficient	Normal	Insufficient
Waist-to-hip ratio	Normal	Low	Low	Normal	High	High	High	High
	Nutritional status of cirrhotics with fluid retention							
	Healthy	**tPEM**	**Underweight**	**PM**	**NWO**	**NWO & PM**	**(S)O**	**(S)O & PM**
BMIc	Normal	Low	Low	Normal	Normal	Normal	High	High
HGS	Normal	Low	Normal	Insufficient	Sufficient	Insufficient	Normal	Insufficient
Ectopic fat marker	Normal	Low	Low	Normal	High	High	High	High

HGS hand grip strength, BMCc body mass index corrected for fluid retention.

Nutritional interventions

Various studies have shown that nutritional interventions are able to improve nutritional status and the nitrogen balance (82, 111, 171-173), leading to an improvement in liver function (174, 175), surrogate variables such as Child Pugh score, serum albumin and serum bilirubin, but also mortality as a most relevant clinical endpoint in cirrhotic patients (174, 175). However, a meta-analysis of such, often short term, studies by Koretz *et al.* (176) showed no effect on survival, duration of hospital stay or the development of HCC nor on the rate of complications such as infections, encephalopathy or bleeding. This is not surprising. It is unlikely that short-term standard nutritional supplementation can improve

nutritional status, let alone cure patients. It also cannot suppress symptoms. Nutritional supplementation can however improve the nutritional status when given long-term. The improved nutritional status can then, in turn, lead to fewer complications and probably longer survival. Two long-term studies have indeed shown a significantly lower incidence of complications (177). A more recent trial also showed that a combination of specific nutritional advice and nutritional supplementation is associated with an improved grip strength. This may indicate an improved protein nutrition status (111), though further research is needed. Short-term interventions are perhaps easier to perform because they are cheaper whereas long-term RCTs studying the effect of these interventions are expensive and difficult to fund. Obtaining ethical approval for any short- or long-term RCT is difficult as it implicates that the malnourished control group does not receive volitional nutrition support. This may also be the reason why most studies exclude severely malnourished patients. Koretz *et al.* (178) and others concluded that this excludes the group of patients that may benefit most from nutritional supplementation.

More recent developments indicate that the timing of protein and energy administration is important. Not only frequent meals during the day but an additional late evening energy and protein enriched snack has been shown to improve the nutritional status directly (111). Adding branched-chain amino acids to the late energy and protein enriched snack may enhance the effect on the nutritional status (3) but their use is controversial (99, 179, 180).

Weight loss in pre-liver transplantation patients does not affect outcome. This may be because uncontrolled weight loss with significant protein loss has different risks; while fat loss may reduce some risks, protein deficiency leads to new risks. When taking the high rates of overweight and obesity and perhaps NWO in patients with liver cirrhosis into account, it is important to emphasize that most patients with liver cirrhosis require protein enrichment and a normal or lowered carbohydrate intake with a low glycaemic load, without energy enrichment. Nutritional advice should also be accompanied with the advice to perform some exercise (supported by a physiotherapist when needed), even when patients are bedridden to maintain muscle mass and prevent or reduce insulin resistance (181).

Current guidelines do not address these issues; nutritional guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN) (166, 182), only recommend a higher intake of energy (35-40 kcal/kg body weight/day) and protein (1.2–1.5 g/kg body weight/day) in malnourished patients with liver cirrhosis. Requirements of healthy individuals are on average for energy 25 kcal/kg/body weight and for protein 0.8 g/kg body weight per day (WHO). Only a very low percentage of patients have tPEM (1-8%), and are indeed in need of a high energy and protein diet. This, in fact, may be another reason why studies on the effect of nutritional interventions, which are based on current guidelines, have not shown favourable results. These guidelines therefore urgently need revision and should take in account the large group of patients with (S)O, PM, MM and their combinations. If these are not taken into account, these guidelines may indeed deteriorate liver disease.

Current guidelines conservatively recommend nutritional counselling only in patients with decompensated liver cirrhosis or with a suspicion of malnutrition. This may be problematic as malnutrition is already highly prevalent in patients with compensated cirrhosis suggesting that the onset of malnutrition may be in the pre-cirrhotic phase of this disease. Furthermore, in general it is easier to maintain the nutritional status than to repair it. Teaching patients preventatively may be more successful and prevent complications to occur and prolong survival. Pre-cirrhotic assessment of the nutritional status is not complicated by possible fluid retention. Apart from this, current guidelines are followed correctly by only 23% of gastroenterologist in Germany, and 41% still believe that an evaluation of the BMI is the best diagnostic tool for detection of malnutrition in patients with liver cirrhosis (183). Considering the current high prevalence of malnutrition in patients with liver cirrhosis, there is little reason to believe that these guidelines are followed more strictly elsewhere.

Conclusion

There is a high prevalence of malnutrition in patients with liver cirrhosis in all Child Pugh classes. However, the prevalence of tPEM, appears to be low (1-8%). Other types of malnutrition, each with specific and high health risks, are far more prevalent. This calls for a differentiation in the definition of malnutrition in these patients. PM (up to 51%), (S)O (up to 61%), the combination of PM and (S)O (up to 71%) and excess fat mass in normal weight patients with or without PM (NWO, up to 60%) are far more prevalent. Furthermore, the combination of PM and liver cirrhosis may promote muscle mass breakdown and enhanced fat storage. The combination of ectopic fat and liver disease may enhance protein deficiency, promoting loss of muscle mass and storage of more fat. All types of malnutrition have an extremely high risk of being accompanied by MM. Combinations of these types of malnutrition therefore lead to exponentially greater health risks.

These highly prevalent types of malnutrition are rarely diagnosed due to the absence of simple markers of these types of malnutrition but also due to a lack of awareness of these conditions. Recent studies have indicated that a diagnosis is possible with a combination of specific simple markers of malnutrition. We propose the use of a combination of the BMI, hand grip strength and waist-to-hip ratio, at least in those without fluid retention. In patients with fluid retention, we propose that BMIc (after validation in outpatients), combined with HGS, which may diagnose all types of malnutrition except the difference between PM and PM with NWO in a clinical setting. These markers, a CT scan or MRI for determining ectopic fat and protein mass, should, for now assess the nutritional status of these patients in a research setting. Whether these markers purely indicate malnutrition or are more general markers of the severity of disease is still uncertain but they are strong indicators of risks and can be improved by nutritional intervention. Routine assessment of the nutritional status, preferably starting at time of diagnosis of liver disease, is crucial. Including the proposed assessment of the nutritional status into scoring systems of severity of disease (Child Pugh and MELD score) may be key in improving their sensitivity and specificity.

Current nutritional guidelines need to be updated urgently as they focus only on tPEM, calling only for both energy and protein enrichment. They do not differentiate between the different types of malnutrition in cirrhosis and following these guidelines may exacerbate liver disease in most patients. This may be one of the reasons why there is little evidence that nutritional advice is effective in these patients. Recent studies have indicated that specific nutritional interventions, even short term, may indeed be effective for patients with (or combination of) PM and (S)O (111), and at preventing malnutrition (4, 184).

Future studies may focus on such preventive and curative short and long-term nutritional interventions based on the true nutritional status of the individual patient. For now, nutritional advice and support based on the true nutritional status with advice on physical activity, even when bedridden, should have a high priority. Loss of high risk ectopic fat mass, while preserving or increasing muscle mass and reducing insulin resistance should be the goal in many patients. A second focus of future research should be on finding a valid marker of ectopic fat that, in combination with BMI and hand grip strength, is able to define the nutritional status in patients with fluid retention in the clinical setting.

In this chapter, the poor nutritional status of patients with end stage liver disease is described, with its severe health consequences. Most patients are not protein and energy deficient but are (S)O or both PM and (S)O and remain largely undiagnosed. These risks are not narrowed down to patient with liver disease but may apply to any patients with any disease if (severely) overweight. Especially in combination with protein malnutrition. Also, current diagnostic tools are not only insufficient in patients with liver disease. They are insufficient in any (S)O and or PM patient with any disease. Future research is also needed to study whether the proposed simple diagnostic markers may be used in patients with diseases other than end stage liver disease. Correct diagnostics may be the starting point of halting the negative effects of all types of malnutrition.

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Chapter 3

Protein energy malnutrition predicts complications in liver cirrhosis

Ellen J. Huisman[1], Evelien J. Trip[1], Peter D. Siersema[1], Bart van Hoek[2] and Karel J. van Erpecum[1]

Departments of Gastroenterology and Hepatology,
University Medical Centre Utrecht[1] and Leiden[2], The Netherlands

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Abstract

Background

Protein energy malnutrition frequently occurs in liver cirrhosis. Hand-grip strength according to Jamar is most reliable to predict protein energy malnutrition. We aimed to determine whether protein energy malnutrition affects complication risk.

Methods

In 84 cirrhotics, baseline nutritional state was determined and subsequent complications prospectively assessed. Influence of potentially relevant factors including malnutrition (by Jamar hand-grip strength) on complication rates were evaluated with univariate analysis. Effect of malnutrition was subsequently evaluated by multivariate logistic regression with adjustment for possible confounders.

Results

Underlying causes of cirrhosis were viral hepatitis in 31%, alcohol in 26%, and other in 43%. Baseline Child–Pugh (CP) class was A, B, or C in 58, 35, and 7%, respectively. Energy and protein intake decreased significantly with increasing CP class, with shift from proteins to carbohydrates. At baseline, according to Jamar hand-grip strength, malnutrition occurred in 67% (n = 56). Malnutrition was associated with older age and higher CP class (CP class A 57%, B 79%, C 100%) but not with underlying disease or comorbidity. Complications occurred in 18 and 48% in well-nourished and malnourished patients, respectively, (P = 0.007) during 13 ± 6 months follow-up. In multivariate analysis, malnutrition was an independent predictor of complications, after correcting for comorbidity, age, and CP score (adjusted odds ratio 4.230; 95% confidence interval 1.090–16.422; P = 0.037). In univariate analysis, mortality (4 vs. 18%; P = 0.1) tended to be worse in malnourished patients, but this trend was lost in multivariate analysis.

Conclusion

Malnutrition is an independent predictor of complications in cirrhosis.

Introduction

Protein-energy malnutrition (PEM) is a frequent phenomenon in liver cirrhosis, occurring in 20% of patients with compensated cirrhosis and in 60% or more of patients with decompensated cirrhosis (1,2). PEM may develop in the early phase of cirrhosis (3), regardless of the underlying cause of the liver disease (4). Its pathogenesis is multifactorial: major contributing factors are inadequate dietary intake, maldigestion, and malabsorption of both macronutrients and micronutrients and abnormal substrate utilization. In addition, reduced synthesis and increased loss of protein specifically contribute to the pathogenesis of PEM (5). PEM is associated with impaired immunity, especially in advanced liver disease. This may increase risk of infection in this patient category with underlying intestinal bacterial overgrowth and impaired intestinal barrier function (6,7). PEM could also increase risk of other complications, such as variceal bleeding, ascites, encephalopathy, and hepatorenal syndrome (8,9). Furthermore, the nutritional state may affect quality of life (10) and, after liver transplantation, graft function and patient morbidity or mortality (11).

Despite its importance, PEM is often underdiagnosed in patients with cirrhosis (12), particularly in the early stages of disease (13). Fluid retention, obesity, or other metabolic changes may interfere with diagnosing malnutrition (14). As a result, there is no easy and decisive parameter for PEM in patients with cirrhosis (15). Although controversial (16), hand-grip strength (HGS) according to Jamar (reflecting muscle mass and therefore protein status) is most often used to assess protein depletion in cirrhotics (17–19). Previous studies indicated that Jamar HGS is highly sensitive but not very specific to diagnose protein depletion (15). In this study, we aimed to (a) determine frequency of malnutrition in a group of patients with liver cirrhosis of various aetiologies and in various stages of disease, with the aid of various complementary methods including Jamar HGS, and (b) to assess in a prospective design, the effects of nutritional state – in particular PEM – on occurrence of complications and survival in these patients.

Patients and methods

Patients

In this prospective study, inclusion criteria were the presence of unequivocal cirrhosis based on a combination of clinical, laboratory, radiologic (ultrasound, MRI scan, computed tomographic scan, Fibroscan) and histologic (liver biopsy) findings and patient consent to participate in the baseline nutritional assessments and follow-up. Exclusion criteria were previous liver transplant and coexistent conditions that could affect nutritional state (e.g. gastrointestinal tract disease, malignancy, HIV positivity) and conditions interfering with determination of nutritional state (e.g. mental retardation, arthritis or other secondary diseases that could affect parameters of nutritional state such as HGS). A total of 99 consecutive patients with cirrhosis visiting the outpatient department of two University Hospitals in the period June 2007–April 2008 were considered for inclusion. Fifteen patients with cirrhosis were excluded because of baseline hepatocellular carcinoma (HCC: n = 5)

or pegylated-interferon-based therapy planned during follow-up (n = 10), considering the potential influence of these conditions on nutritional state. In the remaining 84 patients, baseline dietary history and nutritional state were determined in detail with complementary single and combined parameters. Patients visited the outpatient clinic at 6-month intervals, or more frequently if indicated. Follow-up ended in case of death, transplantation or time of final evaluation. Laboratory tests determined at baseline and at follow-up visits including liver synthetic parameters (albumin, international normalized ratio, prothrombin time), bilirubin and creatinine were determined by standard methods. Complications which had occurred before inclusion were noted. During follow-up, the following complications were registered: new onset ascites (diuretic responsive or refractory), hepatic encephalopathy, oesophageal bleeding, hepatorenal syndrome, spontaneous bacterial peritonitis, other bacterial infections (like pneumonia or urinary tract infection), and HCC. The occurrence of hepatic encephalopathy was based on the Conn criteria as evaluated by the physicians in care of the patient. All complications weighed equally. Transplantation during follow-up was also recorded.

Parameters of nutritional state

Baseline dietary intake was calculated by a specialized nutritionist according to standard methods and compared with the nutritional requirements recommended for patients with liver cirrhosis in the ESPEN guidelines from 2006 (20). Height and weight were obtained with a precision of 1 cm and 0.1 kg (Seca scale), respectively. Fluid retention, ascites, encephalopathy, and other parameters of clinical relevance were estimated by the experienced hepatologist in care for the patient. Baseline nutritional state was determined in detail with complementary single and combined parameters. Single para- meters were (a) BMI corrected for fluid retention (BMIc) (21); (b) mid-arm muscle circumference (MAMC) (22); HGS according to (c) Jamar (17,18) or according to (d) Citec. Combined parameters were (e) body cell mass (BCM) (15) and (f) subjective global assessment (SGA) according to Hasse et al. (23). (a) BMIc was calculated as estimated dry weight/(height)2 (in kg/m2) (24). BMIc cutoff values as suggested by Campillo et al. (21) were used to indicate malnutrition. These cutoff values are 22 kg/m2, 23 kg/m2, and 25 kg/m2 in patients without, with mild, and with tense ascites, respectively. (b) Mid-arm circumference (MAC) and triceps skin fold thickness (TSF) were first measured to the nearest millimetre at the non-dominant arm with a measurement tape and a skin fold calliper with a pressure of 10 g/mm2 of contact surface (Holtain Ltd London, UK). Measurements were taken midway between the tip of the acromion and the olecranon process, with the patient standing in a relaxed position. MAMC was then calculated from MAC and TSF with the formula MAMC = MAC – (p x TSF). The average of three measurements was used. Values of MAMC were compared with those of a healthy reference population (22). (c) Voluntary HGS was measured in the dominant hand by using a calibrated Jamar dynamometer (ProCare, Groningen, The Netherlands) adjusted for sex, age, and height and compared with a healthy reference population (18).

The best of three consecutive measurements was recorded (1 min recovery time between attempts). (d) Pinch power (Citec) was assessed with a pinch gauge (C.I.T. Technics, Centre for Innovative Technics, The Netherlands) to test the isometric muscle strength (in Newtons). Isometric strength is the torque generated by a muscle group when it is not allowed to shorten during contraction, the muscle being made to contract against an immovable load. (e) BCM: Figueiredo et al. (15) found that the combination of MAMC and HGS was the best predictor of the BCM. The combined criteria of a HGS less than 30 kg and a MAMC below 23 cm were reported to exhibit a sensitivity of 94% and a negative predictive value of 97% in identifying patients with a depleted BCM (15). (f) The SGA adjusted for patients with liver cirrhosis by Hasse et al. (23). This parameter comprises weight loss during previous 6 months in combination with changes in diet intake during the week before evaluation and gastrointestinal symptoms, functional capacity and fluid retention at the time point of evaluation. The physical examination focuses on loss of subcutaneous fat, muscle wasting and fluid retention. SGA is classified as normal, mild, moderate or severe malnutrition. Based on previous data (17–19), before the start of the study, we chose baseline HGS according to Jamar to distinguish well-nourished and malnourished patients.

Quality of life survey

Quality of life was assessed using the validated Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) described in detail elsewhere (25). The SF-36 scale does not reflect symptoms particular to certain conditions, but evaluates health comprehensively, and is used for a wide variety of disorders. SF-36 scores range from 0 (lowest) to 100 (highest), with higher scores indicating better health-related quality of life. The SF-36 is composed of 36 questions, which provide a quantitative evaluation for each of eight subscales: physical function, role–physical, bodily pain, general health perceptions, vitality, social function, role–emotional, and mental health (MH). The survey contains four domains in the area of physical health (physical function, role–physical, bodily pain, and general health perceptions) and four in the area of MH (vitality, social function, role–emotional, and MH). Raw scores were transformed into 0–100 scales, with 0 and 100 assigned to lowest and highest possible values, respectively. Higher scores indicate better health. The scales of SF-36 were summarized into two scales: the physical component summary and the MH component summary.

Statistical analysis

Statistical analysis was carried out using SPSS version 15.0 for Windows. Data are given as mean ± SD in case of parametric distribution and also as median and range in case of nonparametric distribution. Differences were tested for statistical analysis by dependent or independent t-test, Pearson w2-test or analysis of variance with Fisher LSD as post-hoc test as appropriate. The Kolmogorov–Smirnov test was used to test for normal distribution. The Mann–Whitney U test or the Kruskal–Wallis test was used if the normality assumption was

not met. The primary endpoints were a complication or end of follow-up.

Complications during follow-up were compared between well-nourished and malnourished groups according to Jamar HGS (17–19). The influence of nutritional status according to Jamar HGS, age, sex, underlying cause of cirrhosis, comorbidity, CP score, and BMI score on complications and mortality during follow-up were first evaluated with univariate analysis using logistic regression. As we were interested only in the effects of nutritional state on complication risk, multivariate logistic regression was subsequently used to adjust for possible confounders: All variables with P-value of less than 0.200 in univariate analysis were entered in the model as covariables. Backward stepwise regression was then used to exclude variables with P value of more than 0.05. Results of logistic regression are presented as adjusted odds ratios (OR) with exact 95% confidence intervals (CI) and two- sided P-values. Differences between Kaplan–Meier curves were tested for statistical significance using the log rank test. A two-sided P-value of less than 0.050 is considered statistically significant.

Results

Patient characteristics

Baseline characteristics of the 84 included patients are given in **Table 1**. The underlying causes of cirrhosis were viral hepatitis in 31%, alcohol in 26%, and other diseases (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, hemochromatosis, Wilson disease) in 43% of cases. Baseline Child–Pugh (CP) class was A, B, or C in 58, 35, and 7%, respectively. Forty-six percent of the patients exhibited significant comorbidity (diabetes mellitus, cardiovascular disease, inflammatory bowel disease). Twenty-nine percent of patients were on the waiting list for transplantation.

Table 1. Baseline characteristics of 84 well-nourished an malnourished with cirrhosis based on Jamar hand-grip strength

	All patients	Well-nourished patients	Malnourished patients	P
Number of patients	84	28	56	
Duration of follow-up (months)	13 ± 5 (1–19)	14 ± 3 (7–19)	12 ± 6 (1–19)	0.049
Etiology				0.462
Viral hepatitis	26 (31%)	10 (36%)	16 (29%)	
Alcoholics	22 (26%)	5 (18%)	17 (30%)	
Other	36 (43%)	13 (46%)	23 (41%)	
Age (years)	55 ± 12 (22–79)	51 ± 13 (23–79)	56 ± 11 (22–77)	0.040
Sex (men)	56 (67%)	20 (71%)	36 (64%)	0.513
Child–Pugh class				0.047
A	49 (58%)	21 (75%)	28 (50%)	
B	29 (35%)	7 (25%)	22 (39%)	
C	6 (7%)		6 (11%)	
Comorbidity	39 (46%)	10 (36%)	29 (52%)	0.164
On transplantation waiting list	24 (29%)	5 (18%)	19 (34%)	0.075
Routine blood tests				
Bilirubin (µmol/l)	44 ± 95: 24 (3–845)	23 ± 14: 18 (7–61)	55 ± 115: 29 (3–845)	0.158
Protrombin activity (INR)	1.22 ± 0.22 (0.90–2.0)	1.15 ± 0.19 (0.96–1.8)	1.26 ± 0.23 (0.9–2.0)	0.066
Albumin (g/l)	35.8 ± 6.5 (20–49)	37.3 ± 5.2 (23.6–47.3)	34.5 ± 6.9 (20.4–49)	0.065
Creatinine (µmol/l)	88 ± 31 (43–247)	82 ± 17 (52–116)	91 ± 35 (43–247)	0.123
BMIc (% of patients with normal BMIc)[a]	25 ± 5 (16–40 (50%)[a]	25 ± 4 (19–37) (61%)[a]	26 ± 5 (16–40) (45%)[a]	0.684
Energy intake (kcal/day)	2058 ± 671 (694–4916)	2395 ± 651 (1181–4916)	1893 ± 622 (694–3978)	0.001
Sufficient	59%	74%	51%	0.045
Protein intake (g/day)	90 ± 31 (18–206)	110 ± 29:(72–206)	79 ± 27: (18–167)	0.000
Sufficient	46%	67%	36%	0.010
Energy % fat	33 ± 7	35 ± 7	32 ± 8	0.142
Energy % carbohydrates	50 ± 9	46 ± 6	52 ± 9	0.021
Energy % protein	17 ± 4	19 ± 3	16 ± 4	0.013
Ratio carbohydrate/ protein intake (energy %)	3.1 ± 1.1: 3.0 (1.3–6.4)	2.6 ± 0.6:2.5 (1.5–3.8)	3.4 ± 1.2:3.2 (1.3–6.4)	0.002
Meal (number/day)	4.9 ± 1.3 (2–9)	4.9 ± 1.3 (2.5–7.5)	4.9 ± 1.3 (2–9)	0.717
Quality of life				
Physical component summary	56 (8–98)	79 (34–98)	43 (8–95)	0.000
Mental component summary	64 (12–98)	74 (29–98)	59 (12–96)	0.066

Data are presented as n (%) or means ± SD (range). In case of non-parametric distribution, medians (range) are also given. [ ] indicates % pts with normal BMIc. P-values for well-nourished versus malnourished group.

Nutritional assessment

Various parameters of nutritional status indicated mal- nutrition in 5–74% of all cases depending on the method used (Jamar 67%, Citec 74%, MAMC 58%, SGA 58%, BCM 39%, BMIc 5%). For most methods, malnutrition tended to be more frequent with higher CP class (**Table 2**). At baseline, 67% of patients (n = 56) were malnourished (CP class A 57%, B 79%, C 100%) and 33% (n = 28) well-nourished according to Jamar HGS. Of note, prevalence of obesity was high in our Dutch patients with liver cirrhosis, independent of CP class: 25% were overweight (BMI overweight (BMIc 25–29.9), 14% were obese (BMIc 30–34.9), 5% severely obese (BMIc 35–39.9), and 1% morbidly obese (BMIc Z 40). Only 5% of patients were severely underweight (below 18.5 kg/m2). BMIc, according to cutoff values of Campillo et al. (21), indicated malnutrition in 25% of cases. At baseline assessment, energy, and protein intake were found to be significantly lower with higher CP class. Most importantly, this phenomenon was accompanied by a shift from protein to carbohydrate intake (**Table 2**). CP class did not significantly affect intake of vegetables, fruit or fiber. Ratio of carbohydrate to protein intake as percentage of total energy intake (energy %) was significantly higher with more severe CP class, and was also associated with malnutrition according to Jamar HGS (**Tables 1 and 2**). No significant difference was found in the intake of fat (energy %) between various CP classes or patients with or without sufficient HGS according to Jamar (**Tables 1** and **2**).

Quality of life

The physical and mental components of the quality of life (SF-36) tended to be lower with increasing disease severity according to CP class without reaching significance (**Table 2**). In malnourished patients according to Jamar HGS, the physical component of the SF-36 was significantly lower ($P < 0.00001$), whereas the mental component tended to be lower ($P = 0.066$; **Table 1**).

Table 2. Nutritional intake and state in cirrhotic patients according to Child Pugh Class.

	Child–Pugh class A	Child–Pugh class B	Child–Pugh class C	P-value (two-sided)
Number	49	29	6	
HGS Jamar sufficient	21 (43%)	7 (21%)	0 (0%)	0.047*,**,***
Citec sufficient	15 (30%)	6 (21%)	1 (17%)	0.563
MAMC sufficient	21 (43%)	13 (45%)	1 (17%)	0.541
SGA sufficient	28 (57%)	7 (24%)	0 (0%)	0.002*,**,***
BCM sufficient	32 (67%)	17 (61%)	2 (33%)	0.278
BMIc (normal)	25 ± 4 (18–37) (53%)[a]	26 ± 6 (16–40) (45%)[a]	24 ± 5 (16–32) (50%)[a]	0.311
Energy intake (kcal)	2200 ± 705 (833–4916)	1982 ± 461 (1087–2712)	1245 ± 630 (694–2133)	0.003**,***
Sufficient	74%	38%	17%	0.002*,**,***
Protein intake (g)	97 ± 32 (18–206)	81 ± 27 (37–141)	59 ± 18 (38–77)	0.014*,***
Sufficient	59%	28%	0	0.005*,**,***
Energy % fat	34 ± 7	32 ± 8	32 ± 7	0.522
Energy % carbohydrates	48 ± 8	52 ± 9	52 ± 11	0.238
Energy % protein	18 ± 3	16 ± 4	16 ± 4	0.232
Ratio carbohydrate/ protein intake (energy %)	2.9 ± 0.93 (1.3–6.1)	3.4 ± 1.2 (1.8–6.4)	3.9 ± 1.4 (1.9–5.0)	0.023*
Fruit intake (pieces)	1.8 ± 1.7 (0–10)	1.5 ± 1.2 (0–5.5)	1.5 ± 1.0 (0–3)	0.706
Sufficient	47%	44%	20%	0.544
Vegetable intake (g)	106 ± 66 (0–270)	98 ± 76 (0–300)	30 ± 23 (0–50)	0.106
Sufficient	25%	22%	20%	0.946
Fiber (g)	25 ± 11 (8–64)	21 ± 7 (8–40)	15 ± 9 (8–28)	0.114
Sufficient	42%	22%	25%	0.216
Meal (number/day)	4.8 ± 1.3 (2–8)	5.2 ± 1.5 (3–9)	5.1 ± 1.5 (3–9)	0.297
Quality of life Physical component summary	60 (9–98)	54 (8–96)	34 (12–96)	0.194
Mental component summary	66 (23–97)	56 (15–98)	43 (12–96)	0.257

Data are presented as n (%) or mean ± SD (range). P-value is calculated with one-way analysis of variance, Pearson $_w{}^2$ or Kruskall–Wallis test. With post-hoc test (Fisher LSD). BCM, body cell mass; BMIc, body mass index corrected for fluid retention; HGS, hand-grip strength; MAMC, mid-arm muscle circumference; SGA, subjective global assessment.
*Significant difference (P < 0.05) for CP class A vs. B. **For B vs. C. ***For A vs. C.

[a] Percentage of patients with normal BMIc.

HGS and complications

Of the six nutritional parameters used, only insufficient Jamar HGS was an independent predictor of complications. Although in univariate analysis, there was a trend for SGA and MAMC to predict complications, this trend was lost in subsequent multivariate analysis. In the well-nourished (n = 28, 33%) and malnourished (n = 56, 67%) groups according to Jamar HGS, follow-up was 14 ± 3 months and 12 ± 6 months, respectively (P = 0.049). Malnutrition according to Jamar was associated with older age and higher CP class but not with underlying disease or comorbidity (**Tables 1** and **2**).

Of the 24 patients on transplant waiting list at baseline, nine (38%) were transplanted during follow-up. During follow-up, 32 patients experienced at least one new complication. At least one complication occurred in 18% and 48% of patients in the well-nourished and malnourished patients, respectively (P = 0.007). The malnourished group tended to experience multiple complications (P = 0.09). Eighteen percent of patients exhibited one complication (14 vs. 20% in well-nourished and malnourished groups), 10% of patients exhibited two complications (4 vs. 13% in well-nourished and malnourished groups), 4% of patients exhibited three complications (0 vs. 5% in well-nourished and malnourished groups), 5% of patients exhibited four complications (0 vs. 7% in well-nourished and malnourished groups), and 2% of patients exhibited five complications (0 vs. 3% in well-nourished and malnourished groups). Individual complications are given in **Table 3**.

Table 3. Complications and mortality during follow-up of 84 well-nourished and malnourished patients with cirrhosis based on Jamar handgrip strength

		According to Jamar hand-grip strength		
	All patients	**Well-nourished patients**	**Malnourished patients**	**P**
Number	84	28	56	
Duration of follow-up (months)	13 ± 5 (1–19)	14 ± 3 (7–19)	12 ± 6 (1–19)	0.049
Complications at follow-up	32 (38%)	5 (18%)	27 (48%)	0.007
New onset ascites	20 (24%)	5 (18%)	15 (27%)	0.365
Hepatic encephalopathy	16 (19%)	0	16 (29%)	0.000
Esophageal bleeding	6 (7%)	0	6 (11%)	0.072
Hepatorenal syndrome	7 (8%)	0	7 (13%)	0.051
Spontaneous bacterial peritonitis	8 (10%)	0	8 (14%)	0.035
Other bacterial infections	11 (13%)	1 (4%)	10 (18%)	0.067
Hepatocellular carcinoma	4 (5%)	1 (4%)	3 (5%)	0.717
Mortality	11 (13%)	1 (4%)	10 (18%)	0.067

Data are presented as n (%) or mean ± SD (range).

In univariate analysis using logistic regression, malnutrition measured with HGS according to Jamar (OR 4.3; CI: 1.4–12.9), CP score (OR 2.0; CI: 1.5–2.9), age (OR 1.03; CI: 0.99–1.07), and comorbidity (OR 0.56; CI: 0.23–1.37) were variables with P-value < 0.2 when comparing patients with and without complications during follow-up (**Table 4**).

Table 4. Univariate analyse of various variables on occurrence of new complications during follow-up in 84 patients with cirrhosis.

	New complications			Mortality		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
Hand-grip strength*	4.3	1.4–12.9	0.010	5.87	0.71–48.4	0.100
Age	1.03	0.99–1.07	0.169	1.08	1.01–1.16	0.022
Sex	1.88	0.71–4.98	0.207	1.22	0.28–5.28	0.795
Etiology	0.78	0.46–1.29	0.316	0.72	0.34–1.51	0.384
Comorbidity	0.56	0.23–1.37	0.200	2.24	0.6–8.33	0.228
CP score	2.04	1.45–2.86	0.000	2.07	1.38–3.1	0.000
BMIc	1.00	0.91–1.10	0.954	1.025	0.91–1.16	0.691

BMIc, body mass index corrected for fluid retention; 95% CI is 95% Confidence Interval; CP, child-Pugh; OR is odds ratio. *according to Jamar

In multivariate analysis with backward stepwise logistic regression, malnutrition was an independent predictor of complications, after correcting for age, comorbidity, and CP score (adjusted OR 4.230; 95% CI: 1.09–16.4; P = 0.037). Sensitivity, specificity, positive, and negative predicted values of insufficient HGS to predict complications in our cirrhotic group were 84, 44, 48, and 82%, respectively. When comparing complication rates during the entire follow-up in well versus malnourished patients for all CP classes, the two curves were significantly different (log rank test, P = 0.003; Fig. 1) and for the subgroup of patients with CP class A compensated cirrhosis (log rank test, P = 0.016), whereas differences did not reach statistical significance in the subgroups with CP class B or C cirrhosis.

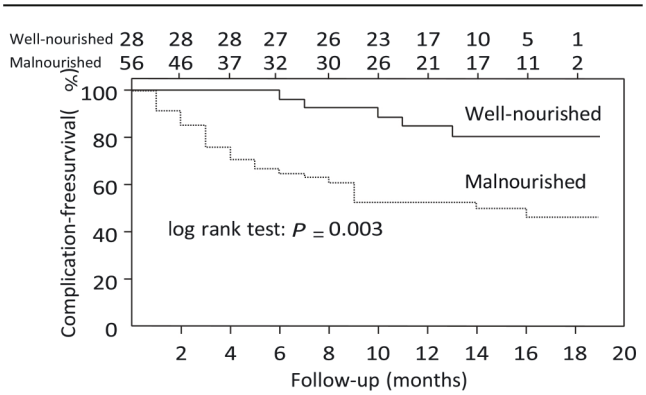

Figure 1. Complication-free survival is significantly lower in malnourished than in well-nourished patients with cirrhosis according to Jamar hand-grip strength test (log rank test, P = 0.003).

Mortality tended to be higher in the malnourished group (4 vs. 18% in the well-nourished and malnourished groups; P = 0.067). A Kaplan–Meier curve revealed a nearly significant difference between the survival of well-nourished and malnourished groups (P = 0.056, log rank test). In univariate analysis, malnourishment tended to be associated with mortality (P = 0.1), but this trend was lost in subsequent multivariate analysis.

Laboratory values at baseline and at end of follow-up in the well-nourished and malnourished groups are given in **Table 5**. Serum albumin levels decreased significantly in both groups, whereas serum creatinine levels increased significantly only in the malnourished group. At end of follow-up, serum creatinine increased significantly more from baseline values in the malnourished than in the well- nourished group (increase + 2.39 vs. + 19.92 mmol/l; P = 0.04). Changes of serum bilirubin (increase at end of follow-up from basal + 6.19 mmol/l and + 12.84 mmol/l in well-nourished and malnourished groups, respectively), albumin (decrease – 1.13 and – 2.17 g/l, respectively), and prothrombin time (change from basal – 0.04 and 0.23, respectively) did not differ significantly between well-nourished and malnourished groups.

Table 5. Laboratory measurements at baseline and end of follow-up in 84 well-nourished and malnourished cirrhotic patients based on Jamar handgrip strength.

	Baseline	End of follow-up	P
Well-nourished patients (n = 28)			
Bilirubin (µmol/l)	23 ± 14: 18 (7–61)	29 ± 31: 18 (7–154)	0.220
Protrombin activity (INR)	1.15 ± 0.19 (0.96–1.8)	1.14 ± 0.14 (0.95–1.41)	0.166
Albumin (g/l)	37.3 ± 5.2 (23.6–47.3)	36.1 ± 5.2 (24.9–45)	0.039
Creatinine (µmol/l)	82 ± 17 (52–116)	85 ± 19 (47–114)	0.333
Malnourished patients (n = 56)			
Bilirubin (µmol/l)	55 ± 115: 29 (3–845)	69 ± 127: 23 (5–544)	0.398
Protrombin activity (INR)	1.26 ± 0.23 (0.9–2)	1.47 ± 1.23 (0.89–8.6)	0.236
Albumin (g/l)	34.5 ± 6.9 (20.4–49)	32.2 ± 7.8 (13–46)	0.037
Creatinin (µmol/l)	91 ± 35: 81.5 (43–247)	107 ± 68: 93 (44–402)	0.020

Data are presented as means ± SD (range). In case of non-parametric distribution, medians are also given.

Discussion

The main findings of this prospective study can be summarized as follows: (a) there is a high prevalence of malnutrition (25–70% depending on method of evaluation) in patients with liver cirrhosis in the Netherlands, even in early stages of the disease; (b) risk of complications is significantly increased in case of malnutrition; (c) intake of both energy and protein decreases progressively with increasing disease severity according to CP class and is associated with PEM. We evaluated PEM particularly with Jamar HGS. Jamar HGS could be affected by polyneuropathy, especially in alcoholic and diabetic patients with cirrhosis. Although not significant, patients with diabetes (11 of 13 patients) and alcoholic cirrhosis (17 of 22 patients) tended to be overrepresented in the malnourished group. Nevertheless, malnutrition according to Jamar was associated with older age and higher CP class but not with cause of underlying liver disease or comorbidity (**Tables 1** and **2**). In addition, Jamar HGS was an independent prognostic factor for complications during follow-up in multivariate analysis, after adjusting for several factors including comorbidity. In line with other studies (19), Jamar HGS proved to be superior to other anthropometric parameters of nutritional state to predict complications. Differences in complication rates between well-nourished and malnourished patients were significant for the subgroup of patients with CP class A compensated cirrhosis, but not for the subgroups with CP class B or C cirrhosis. This phenomenon is not unexpected: in patients with CP class B or C decompensated cirrhosis, other factors than malnutrition such as presence of ascites, bacterial overgrowth, and impaired defence mechanisms against infection are probably predominant in determining complication risk. In addition, the underlying mechanisms for the association between nutritional state and certain complications such as bacterial infections seem evident, whereas this is not entirely clear for other complications such as variceal bleeding. The prevalence of PEM among our Dutch patients with decompensated cirrhosis in our study is very similar to previous data from other countries (26). Of note, a significant proportion of

our patients with compensated cirrhosis also exhibited malnutrition, suggesting nutritional deficiency in relatively early stages of disease. Of special note, prevalence of overweight and obesity (after correction for ascites, BMIc) were high in our Dutch patients with liver cirrhosis, and independent of CP class. Overweight and obesity are known risk factors for development of cirrhosis (27). Severe underweight was found in only 5% of Dutch patients, also independent of CP class. The physical and mental components of the quality of life (SF-36) tended to be lower with increasing disease severity according to CP class, without reaching significance. In contrast, the physical component of the SF-36 was remarkably and highly significantly lower in the malnourished patients according to Jamar HGS. This suggests that malnutrition according to Jamar HGS is associated with excessive overall physical discomfort. The mental component of the SF-36 also tended to be lower in the malnourished group.

The decrease of energy and protein intake with increasing CP class and in HGS insufficiency coincided with a shift from protein to carbohydrate as reflected by increasing ratio of carbohydrate/protein intake (energy %). In contrast, fat intake (energy %) did not change (see **Tables 1** and **2**). Despite the decrease in energy intake, the BMIc did not differ between patients in the three CP classes or between patients with sufficient or insufficient HGS. Together, these findings suggest that inadequate protein intake could explain, at least partly, the high prevalence of PEM in our patients.

Our findings would suggest that dietary interventions could improve PEM and might reduce complication rate. Our findings also suggest that protein enrichment rather than increased calorie intake per se should be emphasized when counselling a patient with cirrhosis. Similarly, the high prevalence of overweight we found, combined with a high prevalence of insulin resistance found in general in cirrhotics (28), indicates that only sufficient intake of carbohydrates with a low glycaemic load is wise in most patients. It also leads us to suggest that protein malnutrition (PM) rather than PEM could describe the nutritional state in most patients with cirrhosis. Indeed, nutritional interventions with protein-enriched supplements have been shown to improve nutritional status and nitrogen balance in cirrhotics (29,30). Especially late-evening supplements seem to be effective: in a recently reported controlled trial, patients with cirrhosis were randomized to either daytime or late evening administration supplements (providing 26 g protein). There was a highly significant improvement of total body protein status in the late evening group, which was not the case in the daytime group (29). These interventions may improve surrogate variables such as CP score, serum albumin, and serum bilirubin and possibly mortality as the most relevant clinical endpoint in patients with cirrhosis (31). Indeed, preoperative nutritional intervention has been reported to reduce infection rates and length of hospital stay after liver transplantation (32). Quality of life may be influenced positively by nutritional intervention as well (10). It should also be realized that nutrient intake and nutritional patterns play a key role in genesis and progression of specific liver diseases (e.g. alcoholic liver injury) (33). Nevertheless, it should be realized, that no prospective trials have unequivocally demonstrated that nutritional intervention and protein- enriched supplements could improve the course of cirrhotic liver disease. In univariate analysis, malnourishment tended to be

associated with mortality (P = 0.1), but this trend was lost in subsequent multivariate analysis (see Results section). Apparently, malnourishment was not an independent factor for mortality in this study. This could relate to the possibility that other factors (e.g. CP score) might be more prominent factors for mortality and/or to the possibility that this study was underpowered to detect an independent effect of malnutrition on mortality.

Nevertheless, factors other than nutritional intake may affect nutritional status in patients with cirrhosis as well. Albumin synthesis seems to parallel liver function, that is the more compromised the liver the less the albumin production rate. Nevertheless, meal-induced albumin synthesis is impaired even in compensated patients with cirrhosis. Skeletal muscle protein synthesis is diminished in cirrhosis and total muscle protein breakdown seems to be increased, thus explaining the reduced muscle mass. Specific degradation of myofibrillar protein may lead to decreased muscle function as well (34,35). Either hormone or substrate resistance may be involved and substances such as cytokines, insulin-like growth factor 1, or leptin may play a role in the reduced synthesis of both albumin and muscle proteins in liver cirrhosis (36). Finally, the physical inactivity associated with severe liver disease may also contribute to muscle wasting. It also remains to be seen whether decreased HGS according to Jamar signifies PM per se or is a more general parameter for the severity of disease. In conclusion, we found a high prevalence of PM in patients with cirrhosis even in the early stages of disease. The prevalence of (often severe) overweight was also high. PEM, as assessed by HGS according to Jamar, was an independent predictor of complications. Whether dietary counselling could reduce PEM, overweight, and the high complication risk associated with these conditions remains to be seen.

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Chapter 4

Bacterial infections in cirrhosis: role of proton pump inhibitors and intestinal permeability

Lotte G. van Vlerken*[,1], Ellen J. Huisman*[,1], Bart van Hoek[†], Willem Renooij[‡], Felix W. M. de Rooij[§],

Peter D. Siersema* and Karel J. van Erpecum*

*Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht,

[†]Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden,

[‡]Department of Surgery, University Medical Center Utrecht, Utrecht,

§Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

[1]These authors contributed equally to this work

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Abstract

Background

Cirrhotic patients are at considerable risk for bacterial infections, possibly through increased intestinal permeability and bacterial overgrowth. Proton pump inhibitors (PPI) may increase infection risk. We aimed to explore the potential association between PPI use and bacterial infection risk in cirrhotic patients and potential underlying mechanisms in complementary patient and animal models.

Materials and methods

Bacterial overgrowth was determined in jejunum of 30 rats randomly allocated to 6-week PPI treatment, gastrectomy or no treatment. In 84 consecutive cirrhotic patients, bacterial infection risk was prospectively assessed and related to PPI use. Intestinal permeability was determined by polyethylene glycol test in 9 healthy individuals and 12 cirrhotic patients.

Results

Bacterial overgrowth was much more common in jejunum of rats treated with PPI or gastrectomy compared to non-treated rats. Twenty-four patients (29%) developed a bacterial infection during a median follow-up of 28 months. Although PPI users tended to experience infection more often than patients without PPI therapy, PPI use was not an independent predictor of bacterial infection (HR 1.2, 95%CI 0.5–3.0, p=0.72), after correction for Child-Pugh class (HR 3.6, 95%CI 1.5–8.7, p=0.004) and age (HR 1.05, 95%CI 1.01–1.09, p=0.02). In cirrhotic patients, 24-h urinary recovery of polyethylene glycols 1500 and 3350 was significantly higher compared to healthy controls.

Conclusions

Although in our animal model PPIs induced intestinal overgrowth, stage of liver disease rather than PPI use was the predominant factor determining infection risk in cirrhotic patients. Increased intestinal permeability may be a factor contributing to infection risk.

Introduction

Patients with liver cirrhosis are at increased risk for developing a broad range of bacterial infections, including spontaneous bacterial peritonitis (SBP), urinary tract infections, pneumonia, skin infections and bacteraemia / sepsis (1-3). In approximately 30% of cirrhotic patients admitted to the hospital a bacterial infection is diagnosed (2, 3). The development of bacterial infections leads to prolonged hospital stay and increased morbidity and mortality (2, 4, 5). Although the exact mechanism by which bacterial infections develop in cirrhotic patients is unknown, increased intestinal permeability may promote bacterial translocation and increase infection rate (6-10). In addition, cirrhotic patients often exhibit complement deficiency, reticuloendothelial system depression and leukocyte dysfunction (1, 11, 12).

Acid-suppressive therapy with proton pump inhibitors (PPIs) or H2 receptor antagonists (H2RAs) could in theory also contribute to the development of bacterial infections, since their use is associated with bacterial overgrowth in the small intestine. H2RAs have been found to increase the risk of bacterial infections (especially pneumonia) in intubated intensive care patients (13). Furthermore, a recent meta-analysis found an increased risk of community-acquired pneumonia in adult PPI users (14). As far as cirrhotics are concerned, four retrospective studies on the association between PPI use and risk of SBP in cirrhotic inpatients with ascites reported contradictory results (6, 15-18). It remains unknown whether acid-suppressive therapy increases specifically the risk of SBP or risk of bacterial infections in general in cirrhotic patients.

In the present study, we explored in a rat model, potential adverse effects of 6-weeks administration of high-dose PPIs on bacterial overgrowth and evaluated the potential association between use of acid-suppressive drugs and risk of various bacterial infections in cirrhotic outpatients. In addition, we assessed intestinal permeability in this patient group.

Methods

Rat study

Animals and conditions

Thirty-two male Wistar rats (Harlan CPB, Austerlitz, the Netherlands), weighing approximately 175 grams, were housed under standard laboratory conditions. Rats were randomly allocated to three experimental groups. Rats in group A (n=10) received omeprazole (Astra Zeneca, Gothenburg, Sweden) in a dose of 400 mg/kg daily by oral gavage, which is equivalent to 80 mg omeprazole administered to humans. Two mg/mL of $NaHCO_3$ (Sigma, Steinheim, Germany) was added to the omeprazole and this was suspended in 0.3 % hydroxypropyl methylcellulose (Sigma, Steinheim, Germany), adjusted to pH 9.0 with NaOH. Rats in group B (n=12) were subjected to gastrectomy with oesophagojejunostomy (GEJ) in order to investigate the effect of total achlorhydria. Twelve rats were operated based on our previous experience that approximately 20% of the rats will be lost due to post-operative complications. Rats in group C (n=10) served as controls. All rats were sacrificed after 6 weeks. Throughout the experiment, animals had access to commercial semi-synthetic rat chow (Hope Farms, Woerden, the Netherlands) and drinking water ad *libitum.*

Surgical techniques

Rats in group B were anesthetized with a gaseous mixture of 3% isoflurane, 64% N2O and 33% O2. Gastrectomy was performed through median laparotomy with the oesophagus attached end-to-site to the jejunum, 3cm distal of the ligament of Treitz. Buprenorphin (0.05 mg/kg) and drinking water were administered directly after surgery, and rat chow was provided ad *libitum* after 24 hours.

Sample collection and analyses of bacterial flora

After 6 weeks, rats were anesthetized and tissue samples (1cm in diameter) were resected from the jejunum (2 cm from the oesophageo-jejunostomal anastomosis). Samples were immediately placed on blood agar, MacConkey agar, Brucella blood agar, Bacteroides bile esculine agar, and kanamycin/vancomycine agar (Becton Dickinson, Alphen a/d Rijn, the Netherlands). Thereafter, animals were sacrificed by decapitation. The plates were transferred to a 37°C incubator and cultured under aerobic (24 and 48 hours) and anaerobic (48 and 120 hours) conditions. After incubation, pure cultures were isolated from the cultured bacteria and these were morphologically analysed using the Vitek system (bioMérieux, Boxtel, the Netherlands) (19).

Prospective cohort study

Patients

Eighty-four consecutive cirrhotic patients from the outpatient clinics of two academic hospitals in the Netherlands were followed prospectively for complications in the period June 2007-June 2010. This prospective cohort is primary aimed to explore relationship between nutritional status and complication rate (20). Diagnosis of cirrhosis was established by a combination of clinical, laboratory, radiological (ultrasound, MR, CT, Fibroscan®) and histological findings. Determination of the aetiology of cirrhosis was made using standard diagnostic criteria. For diagnosis of autoimmune hepatitis, the revised autoimmune hepatitis scoring system was used (21). Alcoholic liver disease was diagnosed in those with regular consumption of at least 60 g / 7.5 units (males) or 40g / 5 units (females) of alcohol daily. Diagnosis of non-alcoholic steatohepatitis (NASH) was based on clinical data (obesity, metabolic syndrome), liver histopathology and absence of alcohol abuse. Cryptogenic cirrhosis was diagnosed when other causes of cirrhosis had been excluded with appropriate tests. Patients with hepatocellular carcinoma, and pegylated interferon-based therapy were excluded since these conditions could interfere with infection risk (n=15). Although acquired immunodeficiency syndrome and other serious diseases were additional exclusion criteria, no patients were excluded for these reasons.

Study design

Patients visited the outpatient clinic at 6-month intervals, or more frequently if indicated. The occurrence of SBP and other bacterial infections, including pneumonia and infection of

skin or urinary tract, was registered prospectively. SBP was defined as granulocyte count > 0.25 x10^9/L in ascites with or without positive ascitic fluid bacterial culture (22, 23). Follow-up ended in case of death, liver transplantation or time of final evaluation (June 1 2010). For the current analysis, charts of all patients were reviewed to investigate if patients were on acid-suppressive therapy during any period of follow-up. Start and end date, dosage, treatment duration and indication for use of acid-suppressive therapy were recorded for all patients. Gastro-oesophageal reflux disease, peptic ulcer disease, and gastro-protection in case of non-steroidal anti-inflammatory drugs (NSAIDs) use were considered valid indications.

Intestinal permeability

Patients

Intestinal permeability was evaluated in 12 cirrhotic patients and 9 healthy individuals. Subjects with gastro-intestinal complaints, renal insufficiency and any co-morbidity other than liver cirrhosis were excluded and subjects were not allowed to use lactulose, NSAIDs, aspirin or alcohol during two weeks prior to the test.

Study design

After an overnight fast, a solution containing 5 g polyethylene glycol (PEG) 400, 5 g PEG 1500 (Bufa Chemical Company, Uitgeest, The Netherlands) and 40 g PEG 3350 (Sigma Chemical Company, St. Louis, MO) dissolved in 100 mL water was orally administered (24-27). After ingestion, subjects fasted during another 6 hours and collected urine during a 24-hour period in two containers (container I: first 8 hours, container II: hours 9-24). Urine samples were stored at -20°C until further analysis by reversed-phase high-performance liquid chromatography as described before (28, 29).

These studies were approved by the Medical Ethical Committee for humans as well as the Animal Experiments Committee under the National Experiments on Animals Act and adhered to the rules laid down in the national law that serves the implementation of "Guidelines on the protection of experimental animals'' by the Council of Europe (1986), Directive 86/609/EC. From human subjects, written informed consent was obtained.

Statistical analysis

SPSS for Windows, version 15.0.1 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Values are expressed as means ± SD for data with Gaussian distribution; otherwise medians with range are used. Proportions were compared using the Pearson $\chi 2$ test or Fisher's Exact test, where appropriate. Continuous variables were compared using the Student's t-test or Mann-Whitney U test, where appropriate. Kaplan-Meier survival analysis with log-rank test was used to compare bacterial infection rates between patients with and without PPI. Cases without bacterial infection were censored at time of liver transplantation, death or end of follow-up. Multivariate Cox regression analysis was used to identify independent

predictors for development of bacterial infection. A two-sided p-value <0.05 was considered statistically significant.

Results

Rat study

All rats in group A (PPI) and C (non-treated) completed the study. Two of 12 rats (17%) treated with GEJ (group B) died before the endpoint of the study due to anastomotic dehiscence (day 4) or stricture at the oesophagojejunostomy anastomosis (day 28). These animals are not included in the analysis. Anaerobic bacterial overgrowth could not be assessed in one PPI-treated rat due to complete overgrowth of the plates by a highly motile swarming Proteus mirablis strain.

Bacterial characterization of bacterial flora

Presence of anaerobic bacteria was more common in jejunum of PPI-treated and GEJ-treated rats compared to controls (**Table 1**). Clostridium perfringens was demonstrated in the jejunum of all GEJ-treated rats and 4/9 PPI-treated rats (44%), and none of the non-treated rats. Bacteroides species were found in 4 GEJ-treated rats (40%), 4 PPI-treated rats (44%) and none of the non-treated rats. A variety of other facultative aerobic bacteria species was also present in the jejunum of PPI-treated and GEJ-treated rats (**Table 1**).

Table 1. Bacteria found in the jejunum of rats treated with a proton pump inhibitor (PPI), gastrectomy plus oesophagojejunostomy (GEJ) or not treated (controls)

Bacterial species	Group A PPI, %	Group B GEJ, %	Group C Controls, %	P-value
Clostridium perfringens	44	100	0	<0.01
Bacteroides spp.	44	40	0	0.05
Escherichia coli	100	50	0	<0.01
Staphyloccus aureus	33	40	0	0.08
Morganella morganii	11	40	0	0.05
Streptococcus spp.	78	30	10	0.01
Lactobacillus spp.	11	0	30	0.14
Enterococcus faecalis	78	40	0	<0.01

Prospective cohort study

Baseline characteristics of the 84 cirrhotic outpatients are given in **Table 2.**

Table 2. Baseline characteristics of 84 cirrhotic patients in prospective cohort study

Characteristic	
Age (years)	55 ± 12
Male gender (n)	56 (67%)
Body weight (kg)	78 ± 19
Aetiology cirrhosis (n)	
Viral hepatitis	26 (31%)
Alcohol	21 (25%)
PSC / PBC	15 (18%)
Autoimmune hepatitis	9 (11%)
Other	13 (15%)
Child-Pugh class (n)	
A	49 (58%)
B	29 (35%)
C	6 (7%)
Ascites (n)	29 (35%)
MELD score	10 (6–27)
On waiting list transplantation (n)	20 (24%)
Diabetes mellitus (n)	18 (21%)
Creatinine (IM)	81 (43–247)
Bilirubin (IM)	24 (3–845)
Prothrombin time (s)	15.1 (12.4-25.5)
Platelets (·109 / L)	116 (9–477)
Serum albumin (g / L)	35.4 ± 6.5

Data represent mean ± SD or median (range). MELD, model for end-stage liver disease.

Use of acid-suppressive drugs

Fifty-two patients (62%) used an acid suppressive agent during the study period (pantoprazole or omeprazole in 51 patients, ranitidine in 1 patient). The vast majority of patients who used acid suppressive drugs was on a once daily dosing regimen (42 patients, 82%) and used a daily dose of 40 mg (44 patients, 86%). None of the patients used their drugs on an "as needed basis". Median duration of acid-suppressive therapy was 30 months (IQR 11–51 months). In 43 patients (83%), no indication for PPI use was documented. In patients with a documented indication, GERD was the most common diagnosis (n=5, 10%), followed by peptic ulcer disease (n=2, 4%), gastric protection in case of NSAID use (n=1, 2%) or a combination of these indications (n=1, 2%).

Bacterial infections during follow-up

After a median follow-up of 28 months (IQR 15–31 months), 16 patients died (19%), due to end-stage liver disease (n=10), hepatocellular carcinoma (n=2) or an unknown cause (n=4). Seventeen patients (20%) underwent liver transplantation, whereas the remaining 51 patients (61%) patients survived without liver transplantation or were on the waiting list for transplantation at end of follow-up. A total of 102 hospitalizations occurred in the total cohort of 84 patients, with 33 patients (39%) without admission, 27 patients (32%) being admitted once during follow-up and 24 patients (29%) with ≥ 2 admissions. The number of patients admitted at least once during follow-up was significantly higher in PPI users compared to patients who did not use a PPI: 75% vs. 38% (p=0.001).

A total of 24 patients (29%) experienced a bacterial infection, requiring treatment with antibiotics. Infection was community acquired in 19 patients (79%) and hospital acquires in 5 patients (21%). Median duration of follow-up at the time of infection was 6 months (IQR 2–21 months). SBP was diagnosed in 9 patients (11%), pneumonia and urinary tract infection both in 3 patients (4%), erysipelas and bacterial gastrointestinal infection both in 2 patients (2%), meningitis in 1 patient (1%), diabetic foot infection in 1 patient (1%), and sepsis of unknown origin in 3 patients (4%). Seven patients (29%) with a bacterial infection died within one month after diagnosis (SBP, n=4; urinary tract infection, n=2; sepsis of unknown origin, n=1). Compared to the patients who did not develop a bacterial infection during follow-up, patients with a bacterial infection were older (mean age 60 years vs. 53 years, p=0.01) and had more advanced liver disease, as expressed by a higher Child-Pugh class (62% vs. 33% Child-Pugh B/C, p=0.02), lower serum albumin concentration (mean 33.2 g/L vs. 36.3 g/L, p=0.05) and prolonged prothrombin time (median 16.7 sec vs. 14.5 sec, p<0.001) (**Table 3**). Of note, follow-up time was significantly shorter in patients with a bacterial infection (median 16 vs. 29 months, p=0.01) (**Table 3**).

Table 3. Characteristics of cirrhotic patients who did vs. did not develop bacterial infection.

	Infection	No infection	
Characteristic	**n= 24**	**n= 60**	**P-value**
Age (years)	60 ± 11	53 ± 12	0.01
Male gender (n)	17 (71%)	39 (65%)	0.61
Body weight (kg)	76 ± 26	79 ± 15	0.62
Child-Pugh class (n)			
A	9 (38%)	40 (67%)	0.02
B	11 (46%)	18 (30%)	
C	4 (16%)	2 (3%)	
On waiting list transplantation (n)	7 (29%)	13 (22%)	0.47
MELD score	13 (6–27)	10 (6–16)	<0.01
Diabetes mellitus (n)	8 (33%)	10 (17%)	0.09
PPI use (n)	17 (71%)	34 (57%)	0.23
Follow-up duration (months)	16 (0.5–31)	29 (0.5–36)	0.01
Prophylaxis SBP (n)[†]	2 (8%)	7 (12%)	0.66
Creatinine (IM)	93 (43–247)	81 (53–172)	0.35
Previous SBP (n)	4 (17%)	4 (7%)	0.22

Data represent mean ± SD or median (range). MELD, model for end-stage liver disease.
SBP, spontaneous bacterial peritonitis.

[†]Norfloxacin 400 mg once daily.

Seventeen patients (71%) who developed a bacterial infection during follow-up used a PPI at the time of infection, compared to 34 patients (57%) in the non-infection group (p=0.23). There were no differences in doses of acid suppressive drugs between patients with infection and those without infection. Median duration of PPI use at the time of infection was 16 months (IQR 2–44 months). In univariate survival analysis, patients who used a PPI tended to develop an infection more frequently than patients without a PPI (**Figure 1**, log-rank test, p=0.11). In multivariate Cox regression analysis, PPI use was not an independent predictor of bacterial infection (HR 1.2, 95% CI 0.5 – 3.0, p=0.72) after correction for Child-Pugh class (HR 3.6, 95% CI 1.5 – 8.7, p=0.004) and age (HR 1.05, 95% CI 1.01 – 1.09, p=0.02). We also conducted the analysis with only SBP as outcome and obtained similar results: in multivariate analysis, Child-Pugh class B/C was an independent predictor of SBP (HR 6.1, 95% CI 1.2 – 30.7, p=0.03), whereas PPI use was not (HR 1.8, 95% CI 0.4 – 9.1, p=0.46).

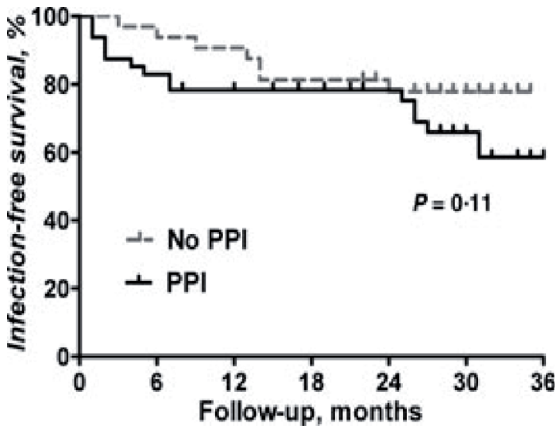

Figure 1. Kaplan–Meier curve comparing bacterial infection rate in 84 cirrhotic patients with vs. without use of PPI (log-rank test P = 0.11). Vertical lines represent bacterial infection, and patients without infection are censored at the time of liver transplantation, death or end of follow-up.

Seventeen patients (20%) died during follow-up, of whom 82% used a PPI compared to 57% in patients still alive at the end of follow-up. In univariate survival analysis, mortality was higher among patients who used a PPI compared to those who did not use a PPI (log-rank test p=0.01). However, PPI use was not significantly associated with mortality (HR 3.2, 95%CI 0.9 – 11.9, p=0.09) after correction for Child-Pugh class B/C (HR 7.5, 95% CI 2.3 – 24.5, p=0.001).

Intestinal permeability

PEG solution was administered to 12 cirrhotic patients and 9 healthy subjects. All subjects had normal renal function. In cirrhotic patients, the underlying cause of cirrhosis was viral hepatitis in 42%, alcohol in 33% and other in 25% of patients. Nine patients had Child-Pugh A liver disease (75%), three patients had Child-Pugh B liver disease (25%). Of the 12 cirrhotic patients, 5 patients (42%) used a PPI compared to none of the control patients.

Figure 2 shows the recoveries of the various PEGs in cirrhotic patients and healthy controls. PEGs 400, 1500 and 3350 were largely excreted within the first 8 hours after the administration of PEG solution (**Figures 2B, D, F**), with the exception of PEG 3350 in cirrhotic patients (**Figure 2F**). No significant differences in 24-hour recoveries of PEG 400 were observed between cirrhotic patients (median 31% (IQR 28–39)) and healthy controls (29% (25–30), p=0.16) (**Figure 2A**). In contrast, 24-h recoveries of PEG 1500 (2.1% (1.5–4.2) vs. 1.3% (0.9–1.7), p=0.02, **Figure 2C**) and PEG 3350 (0.19% (0.13–0.28) vs. 0.11% (0.09–0.18), p=0.02, **Figure 2E**) were significantly higher in cirrhotic patients compared to healthy controls. No significant differences in intestinal permeability between cirrhotic PPI-users and cirrhotic patients who did not use a PPI were found (data not shown).

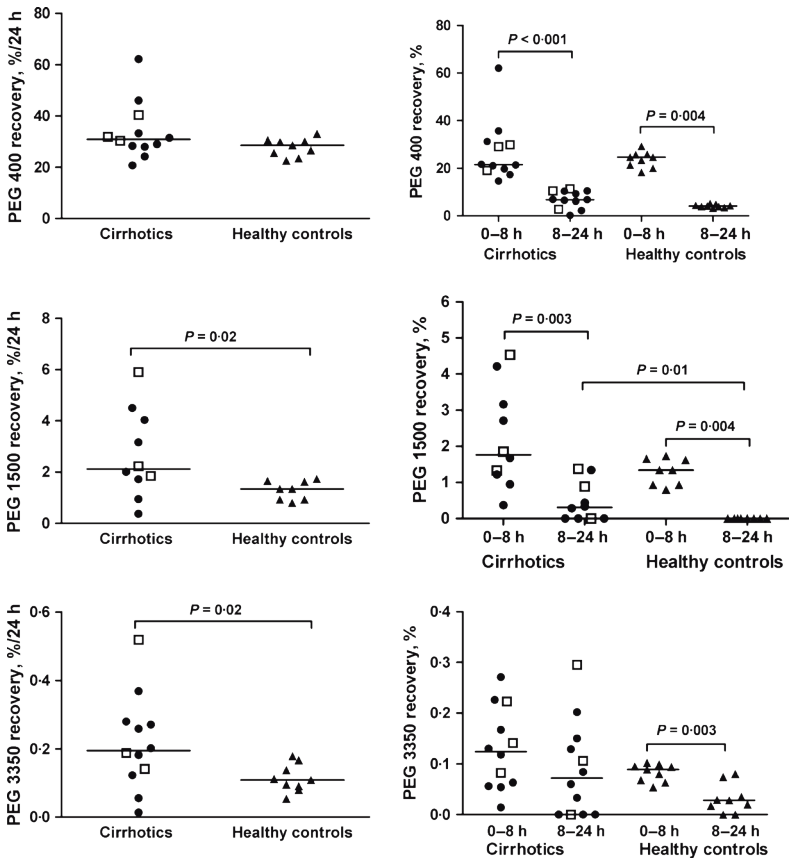

Figure 2. Cumulative 0- to 24-h recoveries of polyethylene glycols with molecular mass 400 (a), 1500 (c) and 3350 (e) as well as relative 0- to 8-h and 8- to 24-h recoveries of the same molecules (b, d and f) in cirrhotics patients compared with healthy controls. Each symbol represents one subject, with circles indicating Child-Pugh A cirrhotics, squares Child-Pugh B cirrhotics and triangles healthy controls. The horizontal line indicates the median value for cirrhotics and healthy controls. Only P-values <0.05 are shown.

Discussion

In this study, we explored a possible association between PPI use and occurrence of bacterial infections in cirrhotic outpatients as well as potential contributing mechanisms. Our experimental animal data indicated bacterial overgrowth in rats treated with PPI, comparable to rats that underwent GEJ. Bacterial infection rate in our cohort of consecutive cirrhotic outpatients was high, but was not found to be related to PPI use. In contrast, state of liver disease was the most important factor in the development of bacterial infections, with Child Pugh B or C patients having a 3-fold increased risk of bacterial infection compared to Child Pugh A patients. Furthermore, increasing age was an independent predictor of bacterial infections. We also conducted the analysis with only SBP as outcome and obtained similar results.

Previous reports on PPI use and infection risk in cirrhotic patients focused on SBP only and -except for one study- only included hospitalized patients with ascites (6, 15-18). In a retrospective matched case-control study among 140 cirrhotic inpatients with ascites, pre-hospital PPI use as well as low ascitic fluid protein content were independent predictors of SBP (15). In line with these results, in a recent retrospective review of 176 cirrhotic inpatients, PPI use was found to be an independent risk factor for the development of SBP beside Child–Pugh class C and high MELD scores (17). In contrast, a retrospective cohort study in 116 consecutive cirrhotic patients with ascites who underwent diagnostic paracentesis upon hospital admission did not find an association between PPI use and development of SBP (16). Furthermore, in the only other available study in cirrhotic outpatients no significant association between use of acid-suppressive therapy and occurrence of SBP was found (6). Differences between various studies may relate to different patient characteristics. For example, a priori chance of infection or SBP is much higher in admitted patients with persistent ascites compared to outpatients. Furthermore, frequency of PPI use varied greatly between these studies (6, 15-17).

Of importance, in our study PPIs were often prescribed in cirrhotic patients without an accepted indication. Although PPIs are generally regarded to be drugs with a good safety profile, previous reports in non-cirrhotic patients indicate that PPI use is associated with an increased risk of community-acquired pneumonia (14), as well as Clostridium difficile infection and other enteric infections (30). Therefore, routine use of acid suppressive drugs in cirrhotic patients is not recommended in the absence of an appropriate indication. Clinicians should constantly re-evaluate the use of PPIs in both cirrhotic inpatient and outpatients.

An alternative explanation for the high infection rate in cirrhotic patients could be increased intestinal permeability. In line with this hypothesis, we found intestinal permeability to be increased in cirrhotic patients compared to healthy controls, in line with earlier reports (9, 10). We used polyethylene glycols of different molecular masses which allow assessment of size-dependent intestinal permeability (24, 25). In contrast to previously used permeability tests as 51Cr-EDTA and sugar absorption tests, the PEG solution contains relatively large compounds (PEG 3350) which mimic the structure of bacterial endotoxins as lipopolysaccharide (24, 25). One might speculate that PPI use among cirrhotic patients might have influenced our results. However, we did not find a significant difference in intestinal permeability between cirrhotic patients with and without PPI.

Aetiology of bacterial infections in cirrhotic patients is probably multifactorial. It is known that intestinal permeability, gut flora and motility are altered in cirrhotic patients (31-34). Furthermore, several abnormalities in immune response have been described in cirrhotic patients (11, 12). Since these risk factors already exist in cirrhotic patients not on PPI therapy, use of PPIs might not have a significant additional effect on infection risk.

In conclusion, although in our animal model PPIs induced intestinal overgrowth, stage of liver disease rather than PPI use was the predominant factor determining infection risk in cirrhotic patients. Increased intestinal permeability may be a factor contributing to infection risk.

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Chapter 5

Preventive versus "on-demand" nutritional support during antiviral treatment for hepatitis C: a randomized controlled trial

Ellen J. Huisman[1,2], Bart van Hoek[2], Hanneke van Soest[3], Karin M. van Nieuwkerk[4], Joop E. Arends[5], Peter D. Siersema[1], Karel J. van Erpecum[1]

[1]Department of Gastroenterology and Hepatology, University Medical Center Utrecht, The Netherlands; [2]Department of Gastroenterology and Hepatology, University Medical Center Leiden, The Netherlands; [3]Department of Gastroenterology and Hepatology, Medical Center Haaglanden The Hague, The Netherlands; [4]Department of Gastroenterology and Hepatology, Free University Medical Center Amsterdam, The Netherlands; [5]Department of Internal Medicine and Infectious Diseases, University Medical Center Utrecht, The Netherlands

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Abstract

Background & Aims

Although antiviral treatment for hepatitis C (HCV) is highly effective, side effects often occur, including weight loss, digestive symptoms, and impaired quality of life. We aimed at exploring the beneficial effects of preventive nutritional support.

Methods

In a randomized controlled trial, 53 HCV patients were allocated to ''on demand'' support (n = 26: nutritional intervention if weight loss >5%) or preventive support (n = 27: regular dietary advice plus energy- and protein-rich evening snack). Nutritional state (including validated Jamar Hand Grip Strength), digestive symptoms (visual analogue score), and quality of life (SF-36 survey) were evaluated at baseline, and after 24 and 48 weeks of peginterferon a-2b and ribavirin treatment.

Results

The primary end point (weight loss at 24 weeks) was reached in 22 patients in both groups. Weight decreased markedly in the ''on demand'' group (decrease at 24 weeks: 5.4 kg or 6.9%, p <0.001), but not in the preventive group (decrease 0.3 kg or 0.3%, p = n.s.). Jamar Hand Grip Strength deteriorated in the ''on demand'' group (from 40.3 ± 15.5 kg to 32.0 ± 13.1 kg, p <0.001) but not in the preventive group (from 40.7 ± 10.4 kg to 39.7 ± 8.9 kg, p = n.s.). Intake of energy, proteins, and fat decreased markedly in the ''on demand'' group but increased in the preventive group. Although digestive symptoms and quality of life deteriorated, impairment was significantly less in the preventive group.

Conclusions

Preventive nutritional advice plus supplementation prevents weight loss and catabolic state during HCV antiviral therapy, with improved digestive symptoms and quality of life.

Introduction

Hepatitis C (HCV) is a leading cause of liver cirrhosis worldwide. By treatment with pegylated interferon plus ribavirin, HCV can be cured in 40–50% of patients with HCV genotypes 1 or 4 and in 80– 90% of patients with other genotypes (1,2). Nevertheless, antiviral therapy is associated with significant side effects. Dose reductions are therefore often needed, compromising the chance of sustained viral response. Moreover, -often severe- weight loss occurs: in previous studies an average weight loss of 9% was reported (3). Weight loss could relate to anorexia due to fatigue, fever, nausea, depression or taste changes during antiviral treatment. Furthermore, interferon-a-based therapy delays gastric emptying, which could lead to upper abdominal discomfort and decreased appetite (4). Although weight loss during antiviral therapy could be associated with catabolic state and protein-energy malnutrition (PEM: a frequent phenomenon in advanced hepatic disease (5)), no data are available on its frequency. Nutritional state could also affect quality of life during anti-HCV therapy (6). The evening supply of an energy- and protein-rich evening snack can supplement free intake and induce an anabolic state in patients with advanced liver disease (7). In the current randomized controlled study, we have explored potential beneficial effects of preventive versus ‘‘on demand’’ nutritional support during anti-HCV therapy.

Patients and methods

Patient selection

Eligible subjects were adults who tested positive for serum HCV antibodies and HCV RNA during at least 6 months and with an indication for antiviral therapy (1,2). Exclusion criteria were Child–Pugh classification B or C, human immunodeficiency virus (HIV) or hepatitis B (HBV) co-infection, unwillingness to use contraception, BMI <18.5, inflammatory bowel disease, significant gastro-intestinal tract surgery, hepatocellular carcinoma or other current malignancies, renal insufficiency (serum creatinine >150 mmol/L) or significant other non-hepatic diseases. The study was conducted according to recommendations of Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent and the protocol was approved by medical ethical commit- tees of all participating centres. This study was registered at ClinicalTrials.gov (identifier NCT00841243).

Study design

This randomized controlled trial was conducted in four centres in the Netherlands during the period 2008–2010. Patients were randomly assigned to the ‘‘on demand’’ or preventive group. Both groups received PEG-interferon alfa-2b (Schering Plough B.V., Maarssen, The Netherlands) 1.5 ug/kg/week subcutaneously and oral ribavirin (Schering Plough B.V.) for 24 or 48 weeks depending on genotype and viral load. Ribavirin dose was 800, 1000, 1200, and 1400 mg/day for body weight <65 kg, 65–75 kg, 76–105 kg, and >105 kg, respectively. Follow-up by treating physicians occurred at 0, 2, and 4 weeks and monthly there- after during treatment, and at three-month intervals for 6 months, post- treatment. Support by a

dedicated nurse practitioner was available if needed. Routine laboratory tests were obtained at each visit and patients were managed according to current guidelines (1,2). At baseline, after 24 and (in case of 48-week therapy) 48 weeks, insulin resistance was evaluated by the homeostasis model assessment (HOMA) index (8). HCV genotyping was performed by nested PCR and hybriziation with Versant HCV Genotype 2.0 Assay (LiPA, Siemens Healthcare Diagnostics, Breda, The Netherlands). Serum HCV RNA testing was performed with COBAS Ampliprep/COBAS TaqMan assays (Roche Diagnostics, Indianapolis IN, USA) on COBAS Taqman. Results were determined quantitatively at inclusion and at week 12 (assay range 43 - 6.9 x 107 IU/ml) and qualitatively at weeks 4, 24, 48, and 72, with a lower detection limit of 15 IU/ml. Baseline low and high viral loads were defined as serum HCV <400,000 or >400,000 IU/ml. Sustained viral response (SVR) was defined as negative serum HCV RNA 24 weeks posttreatment. Adverse events were graded mild, moderate, severe or potentially life threatening according to WHO recommendations (WHO grade 1–4).

Dietary advice and support

During their regular visits, patients in the preventive group received (depending on duration of therapy: 24 or 48 weeks) 7 or 9 Contact Units dietary advice from a specialized nutritionist (30 min of consultation according to Dutch guidelines for mal- nutrition). Dietary advice in combination with dietary supplementation is in general more effective in enhancing short term weight gain and in preventing deterioration of the nutritional status than dietary advice alone (9). Dietary advice including recommendations on meal frequency (5 times/day) and composition (energy- and protein-rich) was therefore combined with an energy- and protein- rich evening snack to be taken daily before bedtime (7). The prescribed Nutridrink protein® (Nutricia, Zoetermeer, The Netherlands) contains 20 g protein, 300 kcal, and 25% of the advised daily amounts of all other essential nutrients. Only in case of significant (>5% of baseline) weight loss, patients in the ‘‘on demand’’ group received dietary advice and supplementation. In both groups, the nutritional state was determined at baseline, after 24 weeks, and, in case of a 48-week treatment, also after 48 weeks as follows: (a) voluntary hand-grip strength (HGS) according to Jamar as measured in the dominant hand with a calibrated Jamar dynamometer (Biometrics, Almere, The Netherlands) adjusted for sex, age, and height and compared to a healthy reference population (10–13). The best of three consecutive measurements was recorded (1 min recovery time between attempts). (b) Pinch power (Citec) was assessed with a pinch gauge (C.I.T. Technics®, Centre for Innovative Technics, The Netherlands) to test the isometric muscle strength (in Newton).

(c) Mid-arm muscle circumference (MAMC): mid-arm circumference (MAC) and triceps skin fold thickness (TSF) were first measured to the nearest mm at the non-dominant arm with a measurement tape and a skin fold calliper with a pressure of 10 g/mm2 of contact surface (Holtain LTD London, UK). Measurements were taken midway between the tip of the acromion and the olecranon with the patient standing in a relaxed position. Mid-arm muscle circumference (MAMC) was then calculated from MAC and TSF with the formula

MAMC = MAC - (p x TSF). The average of three measurements was used. Values of MAMC were compared with those of a healthy reference population (14). Based on previous data (5,10–12), before the start of the study, we chose hand-grip strength (HGS) according to Jamar as the most relevant parameter of nutritional state.

Visual analogue questionnaire of digestive symptoms

Appetite, hunger, the amount of food intake at one meal, nausea, satiety, and stomach ache were measured with a visual analogue scale (VAS) at baseline, after 24 weeks, and (in case of 48 weeks therapy) after 48 weeks (15). Each symptom was rated by a slash on a 10 cm VAS. The VAS lines were anchored at the extremes with words expressing the most positive and negative rating. Subjects marked a single spot on the line and the value was quantified and analysed blindly.

Quality of life survey

Quality of life was assessed employing the validated Medical Outcomes Study 36- item Short-Form General Health Survey (SF-36) (16). SF-36 scores range from 0 (lowest) to 100 (highest). The SF-36 is composed of 36 questions, and contains four domains in the area of physical health and four domains in the area of mental health. Raw scores were transformed into 0–100 scales, with 0 and 100 assigned to the lowest and highest possible values, respectively. Higher scores generally indicate better health. The scales of SF-36 were summarized into Physical Component Summary and Mental Health Component Summary.

Statistical analysis

Our primary end point was weight loss after a 24-week therapy. Our previous study (214 patients) showed average weight loss of 7 ± 6% during a 24-week therapy (17). To show a reduction in weight loss of 60% in the first 24 weeks in the preventive group compared to the ‘‘on demand’’ group, 25 patients needed to be randomly allocated to each group (a = 0.05, power = 0.8 and assuming a drop-out rate of 15%). Secondary end points were other anthropometric parameters, digestive symptom score, and quality of life. Eligible patients were randomly assigned to preventive or ‘‘on demand’’ strategy with stratification for treatment centre. The randomization sequence was computer-generated by an independent subject with blocks of six on a 50/50 basis, and concealed from patients and physicians taking care of the patient. Statistical analysis was performed using SPSS version 15.0 for Windows. Data are given as mean ± SD and/or median and range. Differences were tested for statistical analysis by dependent or independent t- test, Wilcoxon or Mann-Whitney U test, Pearson Chi-square test, two-way repeated measures analysis of variance (ANOVA) with post-hoc Bonferroni correction for multiple comparisons or Kruskal–Wallis test as appropriate. Kolmogorov–Smirnov test was used to test for normal distribution. Two-sided p values <0.05 were considered statistically significant.

Results

Baseline patient characteristics and results of antiviral therapy

Fifty-eight patients were considered for inclusion (Fig. 1). Fifty- three patients were randomized for the ‘‘on demand’’ group (n = 27) or the preventive group (n = 26). There were no significant differences in baseline host or viral characteristics between both treatment arms, except for slightly higher serum creatinine levels in the preventive group (**Table 1**).

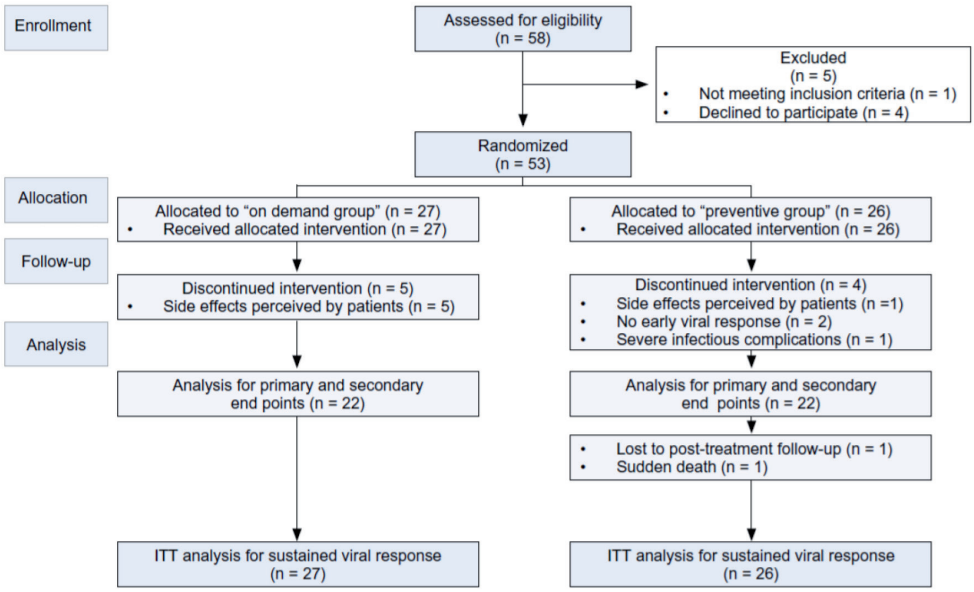


Figure 1 Flowchart. Detailed information on patient number during inclusion, and follow-up

Table 1. Baseline characteristics of 53 chronic HCV patients with ''on demand'' or preventive nutritional support during antiviral therapy.

	All patients (n = 53)	"On demand" group (n = 27)	Preventive group (n = 26)	*p* value
Age, yr (SD)	49 ± 11, 52 (25-69)	50 ± 10, 51 (30-67)	48 ± 12, 51 (25-69)	0.534
Male gender, n (%)	38 (72)	18 (67)	20 (77)	0.544
Weight (kg)	77.0 ± 13.6, 80.0 (46.0-105.0)	77.2 ± 14.8, 79.0 (46.0-105.0)	76.9 ± 12.6, 80.5 (54.0-95.0)	0.929
BMI (kg/m^2)	25.9 ± 4.0, 25.7 (18.9-37.2)	26.1 ± 4.3, 25.6 (18.9-37.2)	25.7 ± 3.7, 25.9 (19.1-32.3)	0.751
HCV genotype, n (%)				
1 or 4	30 (57)	14 (56)	16 (62)	0.477
Others	23 (43)	13 (44)	10 (38)	
Naïve (%)	46 (87)	25 (93)	21 (81)	0.204
Liver disease				
F0-2	28 (53)	14 (52)	14 (54)	0.609
F3-4	24 (45)	12 (44)	12 (46)	
Missing data	1 (2)	1 (4)		
Cause of disease				
IV drug use	13 (25)	9 (33)	4 (15)	0.129
Others	40 (75)	18 (67)	22 (85)	
Baseline viremia				
Low viral load (<400,000 IU/ml)	25 (47)	14 (52)	11 (42)	0.487
High viral load (>400,000 IU/ml)	28 (53)	13 (48)	15 (58)	
Routine blood tests				
AST (U/L)	54 (13-241)	48 (20-241)	75 (13-223)	0.770
ALT (U/L)	86 (29-417)	81 (29-417)	88 (36-212)	0.602
Alkaline phosphatase (U/L)	81 (25-156)	86 (46-140)	68 (25-156)	0.898
Albumin (g/L)	41.2 (30.7-48.0)	41.2 (30.7-48.0)	41.1 (32.8-45.5)	0.840
γGT (U/L)	43 (15-371)	38 (15-213)	56 (20-371)	0.264
Bilirubin (μmol/L)	16 (4-29)	15 (4-29)	16 (8-23)	0.783
INR	1.02 (0.95-1.48)	1.04 (0.95-1.22)	1.02 (0.95-1.48)	0.373
PTT (sec)	13.7 (9.9-17.9)	13.6 (10.0-16.1)	13.7 (9.9-17.9)	0.300
Creatinine (μmol/L)	75 (41-106)	72 (51-87)	76 (41-106)	0.035
Haemoglobin (mmol/L)	9.1 (7.4-10.6)	8.9 (7.8-10.4)	9.4 (7.4-10.6)	0.180
TSH (mlU/L)	1.2 (0.6-3.9)	1.1 (0.6-3.90)	1.5 (0.6-3.90)	0.681
Thrombocytes (x10^9/L)	200 (43-371)	203 (75-325)	198 (43-371)	0.807

Data are presented as n (%), mean ± SD and/or median (range). All routine blood tests are presented as median (range). AST, aspartate aminotransferase; ALT, alanine aminotransferase; cGT, gamma glutamyltransferase; INR, international normalized ratio; PTT, prothrombin time; TSH, thyroid stimulating hormone.

In addition, there were more treatment-experienced patients in the preventive group (5 vs. 2 pts: all previous (PEG) interferon plus ribavirin). Duration of antiviral therapy was 29 ± 14 weeks in the ''on demand'' and 32 ± 12 weeks in the preventive group (p = n.s.). Average peginterferon a-2b dosage (1.55 ± 0.23 and 1.41 ± 0.3 μg/kg/week) and average ribavirin dosage (13.9 ± 1.6 and 14.5 ± 2.1 mg/kg/ day) did not differ. The primary end point (24-week therapy) was not reached in 5 and 4 patients in the ''on demand'' and preventive group respectively, because there was no early viral response at 12 weeks (0 resp. 2 pts),

patient-initiated withdrawal for perceived side effects (5 resp. 1 pt) and severe infectious com- plications in one patient in the preventive group. In the preventive group, one patient was lost to follow-up after end of treatment and one patient suddenly died 5 months post-treatment. Based on intention-to-treat analysis, sustained virologic response was reached in 16/25 and 13/21 treatment-naive patients in the ''on demand'' and preventive group respectively (64% and 62%, p = n.s.). In treatment-experienced patients, sustained virologic response was reached in 2/2 and 1/5 patients in the ''on demand'' and preventive group, respectively. Although there were no significant differences in adverse events according to WHO recommendations, there were significantly less patient- reported side effects in the preventive group (data not shown).

Effects of nutritional advice and supplementation

The primary end point (24 weeks) was reached in 22 patients in both groups. Nutritional parameters for both groups are given in Table 2. Baseline BMI indicated normal weight, overweight, and obesity (BMI 18.5–25, >25–30, and >30 kg/m2) in 54%, 32%, and 14% of the ''on demand'' group and in 54%, 37%, and 9% of the preventive group (p = n.s.).

Table 2. Changes in nutritional parameters in 44 chronic HCV patients with ''on demand'' or preventive nutritional support during 24-week antiviral treatment.

Patient (n=44)	**"On demand" group (n=22)**			**Preventive group (n=22)**		
Nutritional parameters	Baseline	24 wk	*p* value#	Baseline	24 wk	*p* value#
Weight (kg)	76.5 ± 15.8	71.2 ± 14.2	0.000	75.0 ± 12.5	74.7 ± 12.3**	0.648
BMI (kg/m^2)	25.5 ± 4.3	23.7 ± 3.9	0.000	24.9 ± 3.4	24.8 ± 3.2**	0.600
Hand Grip Strength (kg) Sufficient (%) (11) Sufficient (%) (13)	40.3 ± 15.5 11 (50) 17 (77)	32.0 ± 13.1 3 (14) 13 (62)	0.000	40.7 ± 10.4 11 (50) 21 (96)	39.7 ± 8.9** 11 (50)* 20 (91)*	0.462
Pinch Grip Strength (Newton)	116.8 ± 45.0	100.4 ± 38.5	0.015	119.6 ± 27.8	122.2 ± 28.6**	0.531
MAMC	27.9 ± 3.5	27.0 ± 3.4	0.005	27.7 ± 2.3	27.5 ± 2.2	0.437
Albumin	41.1 ± 4.2	39.6 ± 4.5	0.074	40.4 ± 3.9	39.0 ± 5.5	0.073
24 hr urinary creatinine excretion (mMol)	13.1 ± 5.6	12.1 ± 3.1	0.516	12.1 ± 5.1	13.1 ± 4.2	0.076
Energy intake (kcal)	2440 ± 1019	1965 ± 657	0.044	2365 ± 601	2637 ± 401**	0.002
$Protein intake (g)	104 ± 34	81 ± 29	0.011	86 ± 20	142 ± 24**	0.069
$Carbohydrate intake (g)	291 ± 154	263 ± 88	0.306	270 ± 107	275 ± 52*	0.817
$Fat intake, total (g)	88 ± 46	59 ± 32	0.007	79 ± 26	108 ± 29**	0.002
$Energy% carbohydrates	49 ± 11	56 ± 10	0.393	50 ± 9	40 ± 5**	0.849
$Energy% protein	18 ± 5	17 ± 2	0.174	17 ± 5	22 ± 3**	0.002
$Energy% fat	33 ± 10	28 ± 8	0.032	32 ± 7	37 ± 6**	0.022
$Protein/carbohydrate-ratio intake (energy %)	0.40 ± 0.17	0.31 ± 0.08	0.048	0.35 ± 0.14	0.54 ± 0.11**	0.000
‡Fruit intake sufficient (%)	9 (41)	10 (45)	0.952	14 (64)	20 (91)*	0.014
‡Vegetable intake sufficient (%)	7 (32)	3 (14)	0.102	9 (41)	12 (55)*	0.102
‡Fiber intake sufficient (%)	11 (50)	7 (32)	0.025	11 (50)	15 (68)*	0.180

Per protocol data are presented as means ± SD or nr (%).
p values relate to differences between 24 weeks and basal in the same group. Significant differences between the ''on demand'' and preventive group at t = 24 weeks are indicated as /p <0.05 or //p 60.001 (no significant difference at baseline was found for any parameter between both groups).
$ Four patients in the ''on demand'' group and one patient in the preventive group excluded because of insufficient data.
BMI, body mass index; MAMC, mid-arm muscle circumference.
‡Based on Dutch Nutritional Guidelines, Voedingscemtrum, 2011.

In the ‘‘on demand’’ group, weight loss at 24 weeks was 5.4 kg (95% CI 4.0–6.8 kg) or 6.9% of baseline weight (95% CI 5.2–8.6%) (Fig. 2). In the preventive group, weight loss at 24 weeks was 0.3 kg (95% CI -1.0 to 1.5 kg) or 0.3% of baseline weight (95% CI -1.3–1.8%: p <0.001 for comparison between groups). Absolute difference between groups at 24 weeks was 5.1 kg (95% CI 3.3–6.9 kg). Weight loss <1%, 1–5%, 6–10%, and >10% of basal values occurred in 14%, 0%, 68%, and 18% in the ‘‘on demand’’ group and in 73%, 18%, 9%, and 0% in the preventive group (p <0.0001). In the ‘‘on demand’’ group, severity of weight loss was not dependent on baseline weight category (in normal weight, overweight and obese: weight loss 6.3 ± 4.4%, 6.9 ± 2.7%, and 9.7 ± 3.1% resp., p = 0.387).

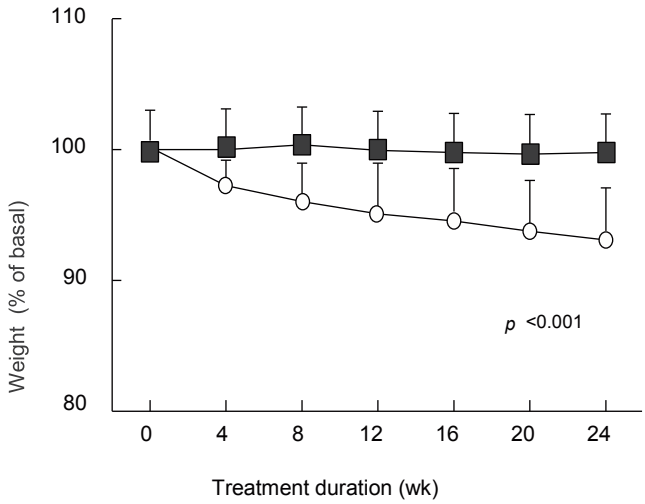


Figure 2. Weight during 24-week antiviral therapy for HCV. In the ‘‘on demand’’ group (n = 22: open circles) there is a significant decrease, which is not observed in the preventive nutritional advice plus supplement group (n = 22: black squares). Significant difference between both groups (p <0.001) and with time (T = 4, 8, 12, 16, 20, 24 weeks all significantly different from basal: two way repeated measures ANOVA). Data are presented as means ±

In addition, beneficial effects of nutritional support occurred in all weight categories and degrees of fibrosis. At 6 months post-treatment, there was only partial recovery of weight loss (increase compared to end of therapy: 3.3 and 1.8 kg in ‘‘on demand’’ and preventive groups respectively). At baseline, Hand Grip Strength according to Jamar was often insufficient, depending on reference values (11,13) (Table 2).

Hand Grip Strength according to Jamar decreased from 40.3 ± 15.5 kg to 32.0 ± 13.1 kg in the ‘‘on demand’’ group (Fig. 3A: p <0.00001) but remained stable (Fig. 3B: 40.7 ± 10.4 and 39.7 ± 8.9 kg at baseline and after 24 weeks) in the preventive group (p <0.001 for comparison between groups at T = 24).

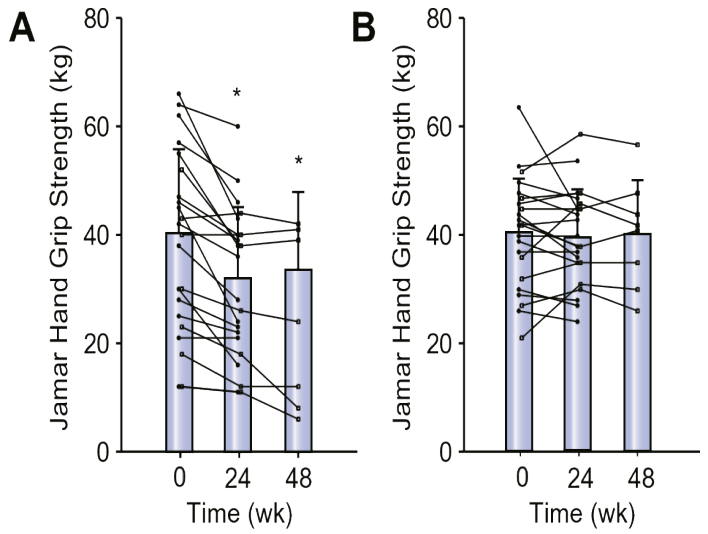


Figure 3. Hand Grip Strength according to Jamar during antiviral therapy for HCV. (A) Significant decrease in the ''on demand'' group. (B) No change in preventive nutritional advice plus supplement group. Black circles indicate patients with 24-week antiviral therapy (n = 15 in the ''on demand'' group, n = 14 in the preventive group). Open squares indicate patients with 48-week antiviral therapy (n = 7 in the ''on demand'' group, n = 8 in the preventive group). Bars indicate means ± SD.

Similar results were obtained for Pinch grip strength and MAMC (Table 2). Decrease of Jamar Hand Grip Strength did not relate to baseline weight category. Intake of energy, proteins, and fat decreased markedly in the ''on demand'' group but increased in the preventive group (Table 2). In the preventive group, ratio protein/carbohydrate intake correlated significantly (R = 0.51, p = 0.02) with change in Jamar Hand Grip Strength at week 24, which was not the case in the ''on demand'' group (Fig. 4).

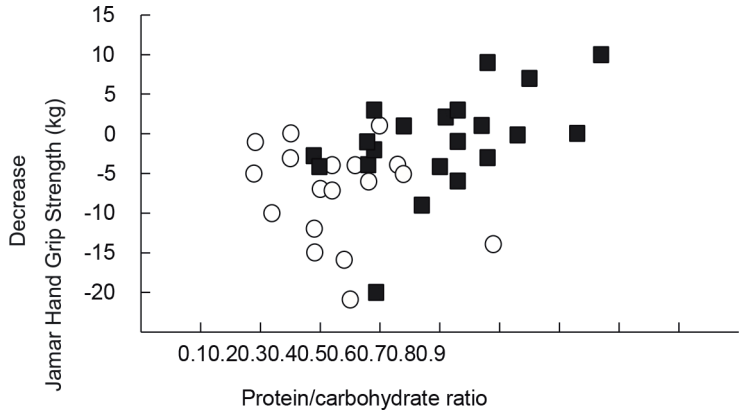
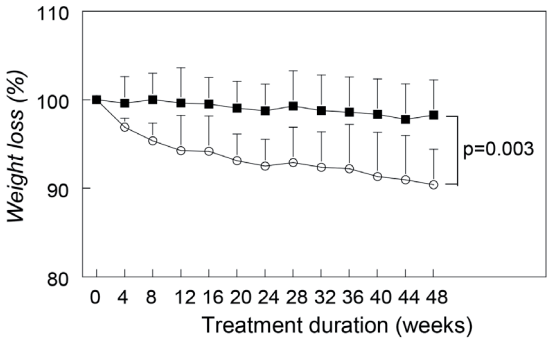


Figure 4. Relation between protein/carbohydrate ratio in diet and decrease of Jamar Hand Grip Strength after 24-week antiviral therapy. Significant correlation in the preventive nutritional advice plus supplement group (black squares: R = 0.51, p = 0.02) but not in the ''on demand'' group (open circles: R = ÿ0.05, p = n.s.). Four patients in the ''on demand'' group and 1 patient in the preventive group are missing because they provided insufficient data to reliably calculate protein/carbohydrate ratios

HOMA index decreased from 1.8 ± 1.7 to 1.4 ± 1.0 in the ''on demand'' group and from 1.5 ± 1.3 to 1.4 ± 1.0 in the preventive group (p = n.s.). Other laboratory data of potential relevance such as vitamin B12, folic acid, cholesterol, and triglyceride levels did not show relevant decreases in either group (data not shown). Seven patients in the ''on demand'' group and 8 patients in the preventive group received 48-week therapy. Preventive nutritional support in this subgroup resulted in persistent beneficial effects on weight loss (Supplementary Fig. 1) and Jamar Hand Grip Strength (Fig. 3). Intake of protein, fat, and protein/carbohydrate ratio increased significantly at 24 and 48 weeks in the preventive group, but decreased in the ''on demand'' group (data not shown).



Supplemental figure 1. Weight during antiviral therapy for HCV in subgroup treated during 48 weeks. In "on demand" group (n = 7: open circles) there is a significant decrease, which is not the case in preventive nutritional advice plus suppletion group (n = 8: black squares). Significant difference between both groups (p <0.003) and with time (two way repeated measures ANOVA). Data are presented as means ± SD.

Digestive symptoms worsened dramatically in the ''on demand'' group, but much less in the preventive group (**Table 3**).

Although quality of life decreased markedly during antiviral therapy, deterioration was much less in the preventive than in the ''on demand'' group (**Table 4**). At 24 weeks, physical and mental component summaries as well as several individual domains were significantly better in the preventive group (**Table 4**). In the ''on demand'' group, percentage weight loss at 24 weeks correlated significantly with decreases of Physical Component Summary (R = 0.57, *p* = 0.006) and Mental Health Component Summary ((R = 0.55, p = 0.009). In the subgroup treated for 48 weeks, beneficial effects of preventive nutritional support on quality of life and digestive symptoms persisted during the entire treatment period (data not shown).

Table 3. Changes in digestive symptoms (according to visual analogue symptom scales) in 44 chronic HCV patients with ''on demand'' or preventive nutritional support during 24-week antiviral treatment.

	On demand" group (n=22)			Preventive group (n=22)			p value#
Symptoms	Baseline	24 wk	*p* value#	Baseline	24 wk	*p* value#	
Do you feel like eating	6.1 ± 2.4	2.6 ± 2.4	0.002	5.3 ± 2.4	4.5 ± 2.1*	0.103	0.019
Are you hungry	5.6 ± 1.9	3.3 ± 2.6	0.006	4.7 ± 2.4	4.4 ± 2.1	0.798	0.166
How much food can you eat	5.3 ± 1.9	3.3 ± 1.9	0.003	5.5 ± 2.1	4.1 ± 1.9	0.021	0.259
Do you experience nausea	0.6 ± 0.9	3.2 ± 3.9	0.016	0.8 ± 1.6	1.2 ± 1.9	0.387	0.225
Do you experience early satiety	1.8 ± 2.7	4.9 ± 3.5	0.008	3.4 ± 3.1	4.3 ± 3.2	0.173	0.607
Do you experience stomach ache	1.1 ± 1.8	2.7 ± 3.6	0.157	0.9 ± 2.3	1.1 ± 2.3	0.384	0.062

Data are presented mean ± SD. # p values relate to differences between 24 weeks and basal in the same group. Significant differences between the ''on demand'' and preventive group at t = 24 weeks are indicated as ⁄p <0.05, with the exact p value given in the last column⁄. No significant difference at baseline was found for any parameter between the two groups.

Table 4. Changes in quality of life (by SF 36) in 44 chronic HCV patients with ''on demand'' or preventive nutritional support during 24-week antiviral treatment.

	On demand" group (n=22)			Preventive group (n=22)			p value#
	Baseline	24 wk	*p* value#	Baseline	24 wk	*p* value#	
Physical functioning	85 ± 19	59 ± 22	0.000	89 ± 16	74 ± 21*	0.002	0.015
Role physical	59 ± 50	13 ± 31	0.016	75 ± 40	40 ± 48*	0.016	0.049
Bodily pain	82 ± 29	61 ± 32	0.003	88 ± 21	74 ± 24	0.049	0.163
General health	62 ± 22	48 ± 20	0.019	61 ± 24	61 ± 23*	0.760	0.047
Social functioning	80 ± 32	40 ± 34	0.000	88 ± 21	72 ± 28*	0.022	0.003
Role emotional	79 ± 38	46 ± 49	0.033	70 ± 45	52 ± 50	0.185	0.755
Mental health	73 ± 19	56 ± 16	0.000	71 ± 15	67 ± 19*	0.363	0.046
Vitality	57 ± 25	29 ± 21	0.001	64 ± 24	47 ± 15*	0.006	0.001
Physical Component Summary	69 ± 23	42 ± 19	0.000	75 ± 19	59 ± 20*	0.001	0.003
Mental Health Component summary	70 ± 20	44 ± 19	0.000	71 ± 20	60 ± 18*	0.011	0.006

Data are presented as mean ± SD. # p values relate to differences between 24 weeks and basal in the same group. Significant differences between the ''on demand'' and preventive group at t = 24 weeks are indicated as ⁄p <0.05, with the exact p value given in the last column⁄. No significant difference at baseline was found for any parameter between the two groups.

Discussion

The major finding of the current study is that preventive nutritional advice plus supplementation prevent catabolic state, digestive symptoms, and impaired quality of life during antiviral therapy, probably related to increased protein intake and/or frequent intake of small meals (4). Beneficial effects of preventive nutritional support on all these aspects clearly persisted after exclusion of treatment-experienced patients from the analysis (data not shown). Hand Grip Strength according to Jamar is a highly-validated parameter of protein energy malnutrition (PEM) and can predict complications in advanced liver disease (5,10–12). We found marked decreases of Jamar Hand Grip Strength and various other anthropometric parameters in the ''on demand'' group, but not in the preventive group. Preventive nutritional support also markedly ameliorated impairment of quality of life. In clinical practice, dose reductions of ribavirin and pegylated interferon are often applied to improve quality of life and avoid sick-leave, with potentially compromised SVR rates. The current study was not designed to detect a difference in sustained viral response. Nevertheless, there were no clear differences in viral outcome if one considers that more treatment-experienced patients were included in the preventive group. Dietary advice combined with dietary supplementation is more effective in enhancing short term weight gain and in preventing deterioration of the nutritional status than dietary advice alone (9). We therefore provided our preventive group with both. For this reason, it cannot be concluded from our data, which component was responsible for the beneficial effects. Further studies on the nutritional impact of telaprevir or boceprevir-containing regimens and value of preventive nutritional interventions under these regimens should be performed in the near future, since these direct-acting agents are taken in combination with meals (including 20-gram fat in case of telaprevir). It remains to be determined whether fat-predominant nutritional intake (as in telaprevir-containing regimens) exerts similar beneficial effects on nutritional state as protein-based nutritional supplement with protein-rich bedtime snack as in our study. Moreover, boceprevir and telaprevir are intended for treatment of HCV genotype 1. For non-genotype 1 patients, dual PEG-interferon-ribavirin combination is expected to remain standard for the next coming years. Although new interferon-free regimens for hepatitis C could potentially affect the relevance of our findings, these are not expected to be introduced in clinical practice in the coming years. In conclusion, in contrast to ''on demand'' nutritional support, preventive nutritional support prevents weight loss and catabolic state, with improved digestive symptoms and quality of life during pegylated interferon plus ribavirin treatment for hepatitis C.

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Chapter 6

Effects of preventive versus ‘‘on-demand’’ nutritional support on paid labour productivity, physical exercise and performance status during PEG-interferon-containing treatment for hepatitis C

Ellen J. Huisman[a], Suzanne van Meer[a], Bart van Hoek[b], Hanneke van Soest[c], Karin M.J. van Nieuwkerk[d], Joop E. Arends[e], Peter D. Siersema[a], Karel J. van Erpecum[a]

[a]Department of Gastroenterology and Hepatology, University Medical Center, Utrecht, The Netherlands [b]Department of Gastroenterology and Hepatology, University Medical Center, Leiden, The Netherlands[c] Department of Gastroenterology and Hepatology, Medical Center Haaglanden, The Hague, TheNetherlands[d] Department of Gastroenterology and Hepatology, VU Medical Center, Amsterdam, The Netherlands[e] Department of Internal Medicine and Infectious Diseases, University Medical Center, Utrecht, The Netherlands

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Abstract

Summary

Background and objective: Deterioration of nutritional status during PEG-interferon containing therapy for chronic hepatitis C can be ameliorated by preventive nutritional support. We aimed to explore whether such support also affects paid labour productivity, physical exercise and performance status.

Methods

In this prospective randomized controlled trial, 53 patients with chronic hepatitis C had been allocated to ''on demand'' support (n = 26: nutritional intervention if weight loss > 5%) or preventive support (n = 27: regular dietary advice plus energy- and protein-rich evening snack) during PEG-interferon containing therapy. Paid labour productivity, physical exercise and performance status were evaluated at baseline, after 24 and (if applicable) after 48 weeks of treatment.

Results

At baseline, 46% of patients performed paid labour and 62% performed some kind of physical exercise. Furthermore, most patients were able to carry out normal activity with only minor symptoms of disease (mean Karnofsky performance score: 94). Decreases of paid labour productivity (—21% vs. —70%, P = 0.003), physical exercise activity (—43% vs. —87%, P = 0.005) and Karnofsky performance scores (—12% vs. —24%, P < 0.001) were less in the preventive than in ''on demand'' group after 24 weeks of treatment. Effects of preventive nutritional support were even more pronounced after 48 weeks.

Conclusions

Preventive nutritional support markedly ameliorates decreases of paid labour productivity, physical exercise and performance status during PEG-interferon-containing treatment for chronic hepatitis C.

Introduction

Chronic hepatitis C (CHC) is a leading cause of liver cirrhosis worldwide. Antiviral therapy for CHC has changed strongly over the past few decades and is nowadays highly effective. Until 2012, combined pegylated (PEG)- interferon plus ribavirin was the standard of care for CHC and resulted in a sustained virological response (SVR) in 40—90% of treatment-naïve patients (1—4). Nevertheless, interferon containing antiviral therapy is associated with significant side effects, which may affect paid labour productivity, physical exercise activity and performance status.

Significant weight loss during interferon-containing antiviral therapy often occurs because of decreased appetite due to fatigue, fever, nausea, depression or taste changes during antiviral treatment (5). Furthermore, interferon-based therapy delays gastric emptying, which could lead to upper abdominal discomfort and less appetite (6). Average weight loss during treatment is reported to be approximately 7% of basal weight (5,7,8). Weight loss may be even more pronounced with triple therapy containing protease inhibitors (9). Severe weight loss during antiviral therapy is accompanied by a catabolic state and protein-energy malnutrition, which is also a frequent phenomenon in advanced hepatic disease (10). A late-evening protein-rich nutritional supplement induces an anabolic state in patients with advanced liver disease (11). In a recently published randomized controlled trial (RCT) (7), we found that preventive nutritional advice plus an energy and protein-rich evening snack before bedtime also prevents deterioration of nutritional status of patients during PEG-interferon-containing antiviral treatment for CHC, with improved digestive symptoms and quality of life. Of note, such nutritional support also prevents catabolic state, as indicated by preserved handgrip strength according to Jamar (12—14), pinch grip strength and other parameters of nutritional state (7).

In previous studies, presence of CHC was associated with less work productivity and more absenteeism (15). These findings were even more pronounced during PEG-interferon containing therapy (16—19). In the current study, we examine the effects of preventive versus ''on-demand'' nutritional advice plus supplementation on paid labour productivity, physical exercise and performance status during PEG-interferon containing treatment for CHC.

Patients and methods

Patient and clinical characteristics

In a previously published RCT performed in the period 2008—2010, we evaluated potential beneficial effects of preventive nutritional support during PEG-interferon containing antiviral treatment for CHC on nutritional state and quality of life (7). Nevertheless, no data on paid labour productivity, physical exercise or performance status have been included in this previous publication. We therefore analysed data on effects of preventive nutritional

support on paid labour activity, physical exercise and performance status. These data had been prospectively collected and were all available in the database of this RCT. In total, 53 patients tested positive for serum hepatitis C virus (HCV)- antibodies and HCV RNA during at least 6 months and with an indication for antiviral treatment (20—22) were randomized for the ''on demand'' group (n = 27) or the preventive group (n = 26). Both groups received PEG-interferon alfa- 2b 1.5g/kg/week subcutaneously and oral ribavirin for 24 or 48 weeks depending on genotype and viral load. Ribavirin dose was 800, 1000, 1200, and 1400 mg/day for body weight < 65 kg, 65—75 kg, 76—105 kg, and > 105 kg, respectively. Duration of antiviral therapy was 29 ± 14 weeks in the ''on demand'' and 32 ± 12 weeks in the preventive group (P = 0.268). Average PEG-interferon -2b dosage (1.55 ± 0.23 and 1.41 ± 0.3g/kg/week) and ribavirin dosage (13.9 ± 1.6 40 and 14.5 ± 2.1 mg/kg/day) did not differ between both groups (7). In the preventive group, patients received dietary advice from a specialized nutritionist during their regular visits as well as an energy- and protein-rich evening snack to be taken daily before bedtime. Dietary advice included frequent energy and protein enriched meals with a high ratio of protein versus carbohydrates during the day. The prescribed Nutridrink protein® (Nutricia, Zoetermeer, The Netherlands) contains 20 g protein, 300 kcal and 25% of the advised daily amounts of all other essential nutrients. Only in case of significant (> 5% of baseline) weight loss, patients in the ''on demand'' group received dietary advice and supplementation. The study was conducted according to recommendations of Good Clinical Practice and the Declaration of Helsinki. Written informed consent was provided by all patients and the protocol was approved by the medical ethical committees of all participating centres. This study was registered at ClinicalTrials.gov (identifier NCT00841243).

Paid labour productivity

For the assessment of paid labour productivity, we asked the patients to provide us with their productivity status at baseline and at the endpoint of 24 weeks and, if applicable, 48 weeks of treatment. Paid labour productivity was defined as paid full time or part time white collar (physically inactive) labour, blue collar (physically active) labour or none. Loss of paid labour productivity was based on percentage of baseline productivity at 24 weeks and, if applicable, 48 weeks of treatment, in only those patients who had any kind of paid labour productivity at baseline and separately for the total group (those with as well as those without paid labour activity at baseline). In addition, unpaid household activities were assessed in all patients without paid labour productivity at baseline.

Physical exercise

For the assessment of physical exercise (outside paid labour working hours), we asked the patients to provide us with their weekly physical exercise activity at baseline and at the endpoint of 24 weeks and, if applicable, 48 weeks of treatment. Patients were divided into the following subgroups according to their physical exercise activity per week:

- none;
- 60 to 150 minutes of low intensity exercise;
- > 150 minutes of low intensity exercise;
- 60 to 150 minutes of high intensity exercise;
- > 150 minutes of high intensity exercise.

Low intensity exercise was defined as walking and leisure cycling. High intensity exercise was defined as strength training, running and intense cycling. Loss of physical exercise was defined as percentage of baseline physical exercise activity at 24 weeks and, if applicable, 48 weeks of treatment, in only those patients with any level of physical activity at baseline and separately for the total group.

Performance status

The Karnofsky performance status (KPS) scale, which ranges from 0—100, was used to evaluate performance status outcomes of patients at baseline, at 24 weeks and, if applicable, 48 weeks of antiviral treatment (23).

Statistical analysis

Continuous data are given as means and standard deviations (SD) or, in case of a non-parametric distribution, as medians and ranges, and discrete variables as absolute and relative frequencies. Differences between the ''on demand'' and preventive groups were tested for statistical significance by independent t-test, Mann—Whitney U-test or Pearson Chi2 test, as appropriate. Pair-samples t-test was used to compare differences between time points in the same group. A two-sided P-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 21.0 for Windows.

Results

Patient and clinical characteristics

Baseline characteristics of all 53 patients who were randomized for the ''on demand'' group (n = 27) or the preventive group (n = 26), and separately for those who reached the primary endpoint of 24 weeks of antiviral treatment (n = 22 in both groups) are given in **Table 1**. Mean age was 49 years and majority of patients was male (72%). Furthermore, 87% of patients were treatment-naïve and half of patients (53%) had only mild liver disease (F0—2). In the patients who were treated for at least 24 weeks (n = 22 in both groups), there were no significant differences in baseline host or viral characteristics between both treatment arms, except a higher proportion of co-morbidity in the preventive group (**Table 1**).

Table 1. Baseline characteristics of 53 chronic hepatitis C patients and separately for the patients with ''on demand'' nutritional support (n = 22) or preventive nutritional support (n = 22) who continued antiviral therapy during at least 24 weeks.

	All patients (*n* = 53)	''On demand'' group (*n* = 22)	Preventive group (*n* = 22)	*P*-value[b]
Age (years), mean (SD)	49 ± 11	51 ± 9	45 ± 11	0.063
Male sex, *n* (%)	38 (72)	15 (68)	17 (77)	0.498
Weight (kg), median (range)	80 (46—105)	78 (69—83)	79 (69—81)	0.841
BMI (kg/m^2), mean (SD)	25 .9 ± 4.0	25 .5 ± 4.3	24.9 ± 3.4	0.751
HCV genotype, *n* (%)				0.365
1 or 4	30 (57)	10 (45)	13 (59)	
Other	23 (43)	12 (55)	9 (41)	
Naïve, *n* (%)	46 (87)	20 (91)	19 (86)	0.635
Liver disease, *n* (%)				0.761
F0—2	28 (53)	12 (55)	13 (59)	
F3—4	24 (45)	10 (45)	9 (41)	
Missing data	1 (2)	0 (0)	0 (0)	
Co-morbidity, *n* (%)	20 (38)	4 (18)	11 (50)	0.026
Cause of disease, *n*				0.082
IV drug use	13 (25)	8 (36)	3 (14)	
Other	40 (75)	14 (64)	19 (86)	
Baseline viremia, *n* (%)				0.353
Low viral load (< 400,000 IU/mL)	25 (47)	12 (55)	15 (68)	
High viral load (> 400,000 IU/mL)	28 (53)	10 (45)	7 (32)	
Routine blood tests, median (range)				
AST (U/L)	54 (13—241)	54 (48—105)	70 (52—95)	0.808
ALT (U/L)	86 (29—417)	106 (81—169)	84 (74—127)	0.552
Alkaline phosphatase (U/L)	81 (25—156)	86 (73—94)	77 (68—97)	0.974
Albumin (g/L)	41.2 (30.7—48.0)	41.2 (39.1—42.7)	40.5 (38.7—42.2)	0.715
GT (U/L)	43 (15—371)	38 (30—76)	53 (29—127)	0.742
Bilirubin (mol/L)	16 (4—29)	14 (13—19)	16 (13—21)	0.783
INR	1.02 (0.95—1.48)	1.02 (1.01—1.08)	1.04 (1.02—1.17)	0.359
PTT (s)	13.7 (9.9-17.9)	13.7 (12.7-14.1)	13.7 (12.5-14.6)	0.977
Creatinine (mol/L)	75 (41—106)	72 (65—76)	75 (62—84)	0.172
Haemoglobin (mmol/L)	9.1 (7.4—10.6)	8.9 (8.5—9.4)	9.3 (9.0—9.8)	0.307
TSH (mIU/L)	1.2 (0.6—3.9)	1.1 (1.1—2.1)	1.6 (1.2—2.3)	0.759
Thrombocytes (×10^9/L)	200 (43—371)	206 (179—236)	212 (170—257)	0.867 0.579

	All patients (*n* = 53)	''On demand'' group (*n* = 22)	Preventive group (*n* = 22)	*P*-value[b]
Paid labour productivity, n (%)				
None	29 (54)	11 (50)	11 (50)	
Full time white collar	8 (15)	3 (14)	4 (18)	
Full time blue collar	10 (19)	6 (27)	4 (18)	
Part time white collar	3 (6)	0 (0)	2 (9)	
Part time blue collar	3 (6)	2 (9)	1 (5)	
Unpaid household (%) activities, *n*	*n* = 29	*n* = 11	*n* = 11	0.193
Yes	13 (45)	6 (55)	3 (27)	
None	16 (55)	5 (45)	8 (73)	
Physical exercise, *n* (%)				0.953
None	20 (38)	6 (27)	8 (36)	
Low intensity, 60—150 min/week	5 (9)	2 (9)	2 (9)	
Low intensity, >150 min/week	16 (30)	7 (32)	7 (32)	
High intensity, 60—150 min/week	2 (4)	1 (5)	1 (5)	
High intensity, > 150 min/week	10 (19)	6 (27)	4 (18)	
KPS score, mean (SD)	94 (9)	94 (10)	94 (8)	0.913

Data are presented as n (%), mean ± SD and/or median (range). All routine blood tests are presented as median (range); KPS: Karnofsky performance status. a In only those patients without paid labour productivity at baseline (n=29). b P-value applies to differences between the ''on demand'' and preventive groups.

Effects of preventive nutritional support during antiviral treatment on paid labour productivity

At baseline, paid labour was performed by 24 of the 53 patients (46%): 15% performed full time white collar labour, 19% full time blue collar labour, 6% part time white collar labour and 6% part time blue collar labour. There were no significant differences in paid labour productivity between the ''on demand'' and preventive groups (Table 1). Of the patients without paid labour productivity at baseline (n = 29), 13 patients (45%) performed unpaid household activities.

Data on paid labour productivity during antiviral therapy are given in Fig. 1A and B. After 24 weeks of treatment, paid labour productivity decreased in both groups, but loss of paid labour productivity was significantly larger in the ''on demand'' group (—70%) than in the preventive group (—21%) (P = 0.003) (Fig. 1A and B), based on only those patients with any paid labour at baseline (n = 22). After 48 weeks of treatment this difference was even greater: —89% in the ''on demand'' group vs. —17% in the preventive group (P = 0.023) (Fig. 1A and 1B). When the total group (n = 44) was taken into account regardless of paid labour productivity at baseline, mean paid labour productivity changed with —35% vs. —6% after 24 weeks of treatment (P = 0.018) and with —8% vs. 0% after 48 weeks of treatment in the ''on demand'' and preventive groups, respectively (P = 0.079).

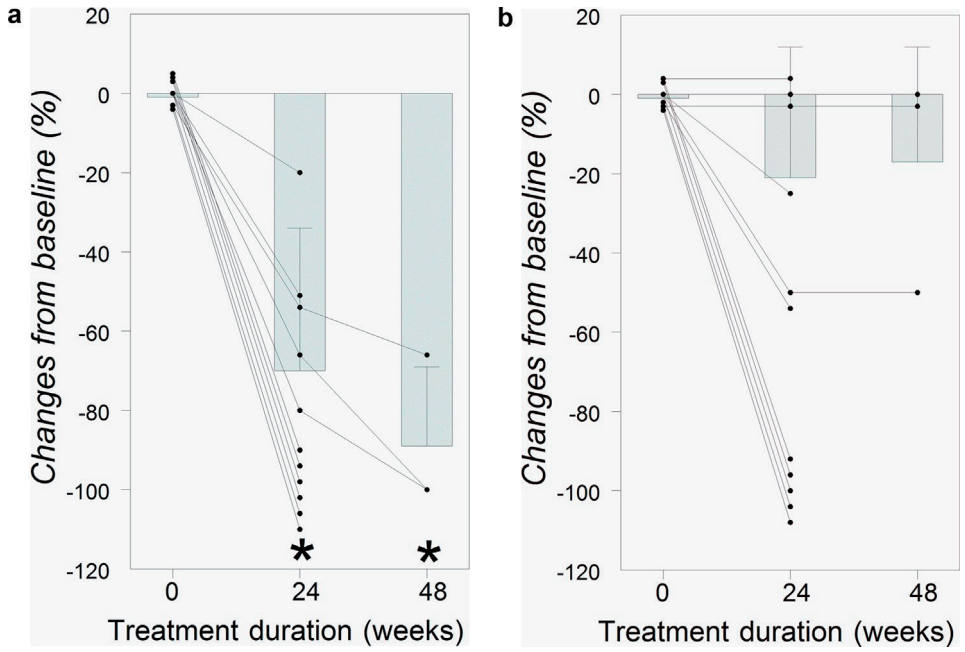

Figure 1. Paid labour productivity as percentage of baseline in patients with chronic hepatitis C with ''on demand'' nutritional support (a) or preventive nutritional support (b) at 24 and (if applicable) 48 weeks of antiviral treatment (n = 11 in both groups, only patients with any paid labour activity at baseline included). Preventive nutritional support significantly decreases loss of paid labour activity. *Indicates significant decrease from baseline in the same group. Dots indicate individual patients connected with lines, bars indicate means with standard deviations. For clarity, some individual points at baseline are depicted slightly above or below zero and error bars positioned upward.

Of the six patients with only unpaid household activities at baseline in the ''on demand'' group, only one continued performing unpaid household activities during the first 24 weeks of treatment. After 48 weeks, all three patients in the ''on demand'' group stopped performing unpaid household activities. In contrast, in the preventive group, two of the three patients with only unpaid household activities at baseline continued performing unpaid household activities and the third patient even had started full time white collar paid labour during the first 24 weeks of treatment. After 48 weeks two of these patients still performed part time white collar labour or unpaid household activities, respectively.

Effects of preventive nutritional support during antiviral treatment on physical exercise

At baseline, many patients (38%) performed no physical exercise at all, 9% had 60 to 150 minutes of low intensity exercise per week, 30% had > 150 minutes of low intensity exercise per week, 4% had 60 to 150 minutes of high intensity exercise per week and 19% had > 150 minutes of high intensity exercise per week (**Table 1**). In patients who received at least 24 weeks of treatment no significant differences in baseline physical exercise activity were found between the ''on demand'' and preventive groups (**Table 1**). Degree of physical exercise

decreased after 24 and 48 weeks of treatment in both groups. Nevertheless, in the preventive group, this reduction was significantly smaller than in the ''on demand'' group. At 24 weeks of antiviral therapy, physical exercise had decreased with 87% in the ''on demand'' group and with 43% in the preventive group (P = 0.005) (Fig. 2A and B). In the subgroup of patients with 48 weeks of therapy, decrease of physical exercise at 48 weeks was 90% in the ''on demand'' group and 0% in the preventive group (P = 0.027) (Fig. 2A and 2B). These decreases were calculated based on only those patients with any physical exercise activity at baseline (n = 30). When the total group (n = 44) was taken into account regardless of physical activity at baseline, physical exercise was decreased with 64% and 25% at 24 weeks of treatment (P = 0.001) and with 64% and 9% at 48 weeks of treatment (P = 0.090) in the ''on demand'' and preventive groups, respectively.

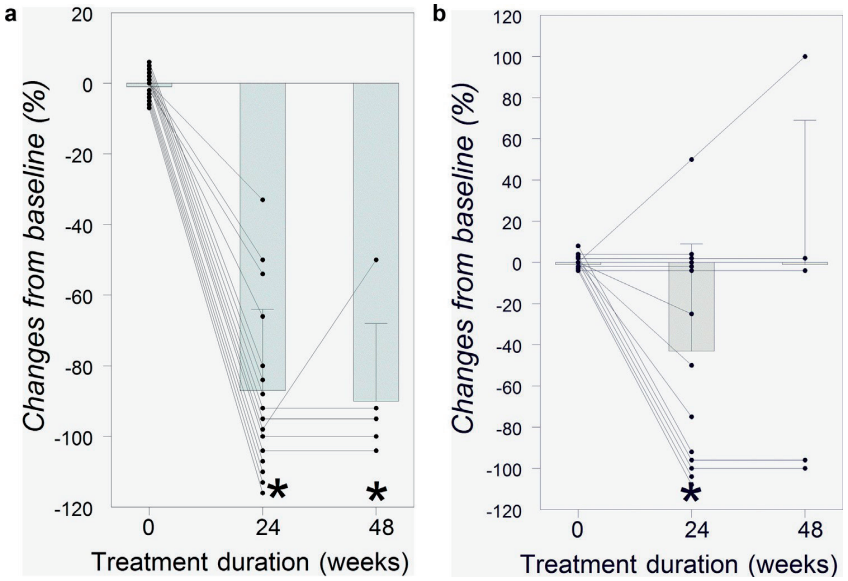

Figure 2. Physical exercise as percentage of baseline in patients with chronic hepatitis C with ''on demand'' nutritional support (a) or preventive nutritional support (b) at 24 and (if applicable) 48 weeks of antiviral treatment (n = 16 and 14 ''on demand'' and preventive groups, only patients with any physical activity at baseline included). Preventive nutritional support significantly decreases loss of physical activity. *Indicates significant decrease from baseline in the same group. Dots indicate individual patients connected with lines, bars indicate means with standard deviations. For clarity, some individual points at baseline are depicted slightly above or below zero and error bars positioned upward.

Effects of preventive nutritional support during antiviral treatment on performance status

At baseline, there were no significant differences in performance status between patients in those ''on demand'' and preventive groups who received at least 24 weeks of treatment. Mean KPS score was 94 ± 10 in the ''on demand'' group and 94 ± 8 in the preventive group, indicating that most patients were able to carry out normal activity with only minor symptoms of disease (Table 1). After 24 weeks of treatment, performance status decreased

in both groups, but this decrease was significantly higher in the ''on demand group'' (—24%) than in the preventive group (—12%) ($P < 0.001$). Similar results were found after 48 weeks of treatment (decrease of 28% in the ''on demand'' group and of 15% in the preventive group, $P = 0.017$).

Discussion

Presence of CHC is associated with significant impact on paid labour productivity, physical exercise and performance status with further deterioration during PEG-interferon containing therapy, as underscored in the current work. A major finding of our study is that preventive nutritional advice plus supplementation decreases such loss of paid labour productivity, physical exercise activity and performance status during antiviral therapy for CHC. Interestingly, another study previously reported that acetyl-l-carnitine supplementation during PEG-interferon-containing anti-CHC therapy decreases fatigue and increases quality of life (24). Recently, it was suggested that acetyl-l-carnitine supplementation also reduces loss of work productivity during anti-CHC therapy (25).

Several studies have investigated the impact of CHC infection on work impairment in a large number of participants (15,19,26—30). Similar to our findings, proportion of CHC patients being unemployed in absence of antiviral therapy was high in these studies (range: 7—74%). Furthermore, CHC-infected workers reported higher levels of overall work impairment than controls (15,19,26—30). Other studies evaluated the effect of anti-CHC therapy on work impairment. In line with our results, work productivity decreased strongly in patients receiving interferon-containing antiviral therapy. During anti-CHC treatment, patients reported more absence days and lower productivity compared to baseline or untreated CHC patients (15—17,31,32). For example, Aggarwal et al. reported a mean increase in number of absence days of 3 days compared to baseline during the previous month after 12 weeks of anti-CHC therapy. Furthermore, more than 50% of patients reported decreased productivity (17). Brook et al. (16) reported lower numbers: CHCemployees who received antiviral treatment had 0.52 more health-related work absence days than non-treated CHCemployees, missing an average of 1.27 workdays monthly. Furthermore, treated CHC employees had 12% fewer units processed per hour worked than those without treatment, but this difference was not statistically significant (16). On the other hand, reaching SVR resulted in improvement of paid labour productivity with less absenteeism than in nonresponders (15,31,33). Previous studies also demonstrated that CHC-patients in general perform less physical exercise than non-CHC subjects (28,30). In our study, proportion of patients who performed no physical exercise at baseline was 38%. During antiviral therapy, physical exercise and Karnofsky performance status decreased strongly in patients without preventive nutritional support. These findings are in line with other studies reporting a decrease in the physical component score of the SF-36 quality of life questionnaire during interferon-containing treatment for CHC (31,32).

In general, productivity is defined as an overall measure of the ratio of the volume of output to the volume of inputs (i.e. units of work processed per hour). Measurement of labour input can therefore be seen as a rough estimation of labour productivity. The true productivity depends on multiple factors (34). Moreover, similar to the current study, most studies regarding impact of CHC infection and antiviral therapy on work impairment used patient reported instead of objective measures, which may introduce measurement error and bias (15).

Results of the current study were validated in a retrospective group of 111 CHC patients under care in our hospital in the period 2011—2014. In line with findings of the current study, only half of patients performed paid labour at baseline. Furthermore, there was also a strong decrease in paid labour productivity after 24 and 48 weeks of PEG-interferon containing antiviral therapy (—51% and —57%, respectively). Most patients in this group performed physical exercise at baseline. However, there was a dramatic decrease in physical exercise: proportion of patients without any physical exercise increased from 14% at baseline to 54% and 77% after 24 and 48 weeks of treatment, respectively. Although percentages slightly differ between this group and the current study, decreases in paid labour productivity and physical exercise during antiviral therapy are large.

The potential underlying mechanisms for the beneficial effects of nutritional support during antiviral therapy on paid labour productivity, physical exercise and performance status may be an improved nutritional state and higher quality of life, as demonstrated previously (7). In the ''on demand'' group of our RCT, there was a trend towards a higher loss of paid labour productivity after 24 weeks of treatment in those patients who performed blue collar labour at baseline than in those with white collar labour (data not shown).

Preventive nutritional support during antiviral therapy and its beneficial effect on paid labour productivity may theoretically be cost-effective. According to the current study, based on an average income of 28,400 euro in 2010 in The Netherlands (data from Central Bureau of Statistics), nutritional advice and support would lead to a reduction in costs due to loss of paid labour productivity of 6436 euro per patient per 24 weeks of treatment. On the other hand, in the Netherlands total costs for preventive nutritional advice plus evening supplementation during 24 weeks of antiviral therapy are only approximately 660 euro per patient.

Paid labour status is influenced by multiple factors, such as patient preference, co-morbidity and age. Indeed, patients with CHC may have several comorbidities that limit ability to work. For example, IV drug use is a common mode of transmission of CHC and is associated with psychiatric conditions (35). Furthermore, in the current study, two patients had haemophilia and these patients may be restricted by joint problems to perform blue collar labour. Only one patient in the ''on demand'' group and none in the preventive group was ≥ 65 years of age and did not have paid labour at baseline.

Recently, several new generation direct-acting antivirals (DAAs) have been approved. Therefore, interferon-free treatment strategies for CHC are nowadays possible, which are

more effective and better tolerated (36—39). As a result, the role of interferon containing in CHC treatment will be limited in the future. However, in specific geographical regions, such as developing countries and other economically deprived regions, interferon-containing antiviral therapy may still be a reasonable option due to excessive costs of the new DAAs (39). Furthermore, results of the new treatment regimens in genotype 3-infected patients have been suboptimal (40).

According to a recent publication (41), work productivity may be less affected by dual therapy with sofosbuvir and ribavirin than with triple therapy with sofosbuvir, ribavirin and PEG-interferon. Nevertheless, proportion of patients with paid labour did not decrease during treatment in either group. Impairment in work productivity disappeared within 12 weeks after end of treatment, but recovery took longer in patients who received interferon-containing therapy (41). Based on analyses of four phase 3 clinical trials of sofosbuvir, the new interferon-free treatment regimens lead to only a minor decrease in health-related quality of life, including the physical component score (42).

Our study has several strengths and limitations. Most important, this study revealed the significant impact of preventive nutritional advice and support on paid labour productivity, physical exercise activity and performance status during PEG-interferon-containing antiviral therapy for CHC, which was not well appreciated in the past. Data was prospectively collected and patients were randomly assigned to the preventive vs. ‘‘on demand’’ groups. On the other hand, as mentioned above, data on paid labour status, physical exercise and performance status relied on patient-reported measures. Finally, dietary advice combined with dietary supplementation is more effective in enhancing short-term weight gain and in preventing deterioration of the nutritional status than dietary advice alone (43). Since our preventive group received both, it cannot be concluded from our data, which component was responsible for the beneficial effects.

In conclusion, preventive nutritional advice and support decreases loss of paid labour productivity, physical exercise and performance status during PEG-interferon-containing treatment for CHC.

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Chapter 7

General summary, recommendations and suggestions for future research

Liver diseases are highly prevalent in the Western world and while death rates of most other diseases, such as heart disease and many cancers, have decreased at least partly due to large investments in health care, standardized mortality rates of liver diseases have increased up to 400% in the last decades (since 1970). In younger patients, this increase is even higher, up to 500% (1).

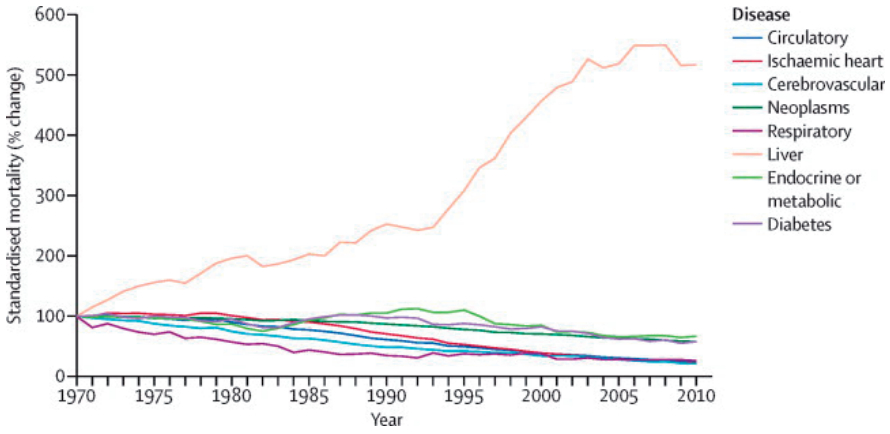

Figure 1. **Standardised UK mortality rate data**

Data were normalised to 100% in 1970, and subsequent trends plotted using the software Statistical Package for the Social Sciences. Data are from the WHO-HFA database. Analysed by Nick Sheron (September, 2013). With permission of the author and publisher.

End stage liver disease, or cirrhosis, is the endpoint in patients who have chronic progressive liver disease. Chronic progressive liver disease has numerous aetiologies, of which heavy consumption of alcohol, chronic hepatitis C infection and non-alcoholic fatty liver disease are the most common in Western societies. It is an often slowly progressing disease in which inflamed and frequently steatotic (fatty degeneration) liver cells are eventually replaced by scar tissue. This process is called fibrosis and it is characterized by distortion of the blood flow through the liver, leading to an increased intrahepatic resistance and portal tension. Clinical signs of liver failure are found when more than 80-90% of liver cells are destroyed (2) and include portal hypertension, leading to formation of oesophageal varices predisposing to bleeding (Fig. 2), as well as renal impairment, water and salt retention, with oedema and ascites (Fig. 3, abdominal fluid retention), and increased cardiac output.

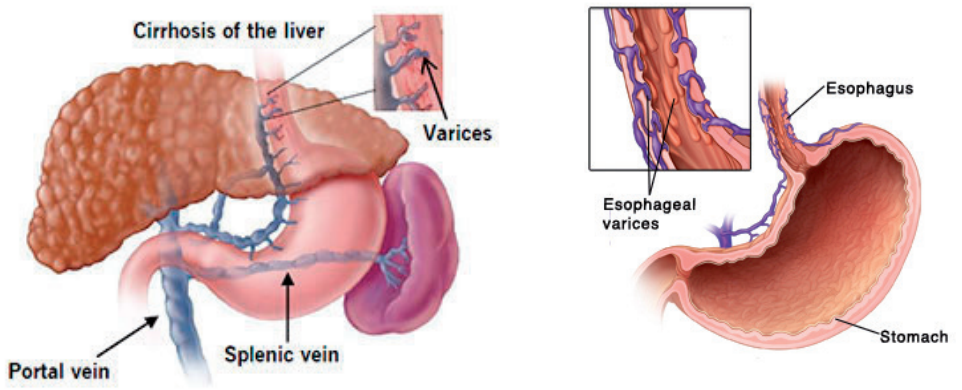

Figure 2. How liver disease leads to bleeding varices

High blood pressure in the portal vein pushes blood into the surrounding blood vessels including those in the oesophagus. The extra blood causes the veins in the oesophagus to swell. These enlarged veins, called varices, can break open and bleed.
http://my.clevelandclinic.org/services/head-neck/diseases-conditions/hic-esophageal-varices and https://www.fairview.org/HealthLibrary/Article/40442, Reprinted with permission.

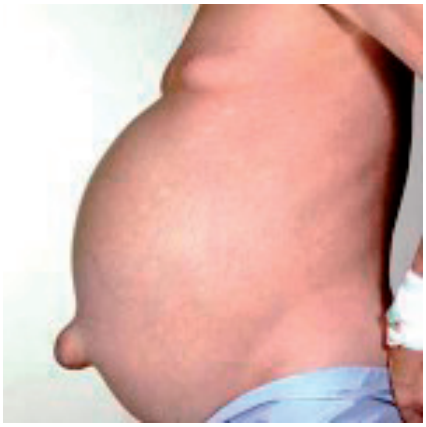

Figure 3. Ascites or the build-up of fluid in the abdominal cavity is a common complications of liver cirrhosis and usually develops when liver functions starts to fail. Less visible fluid retention can occur in earlier stages, interfering with markers measuring malnutrition.

Fibrosis also affects the many (more than 500) functions that a healthy liver should perform. In general, it affects and distorts the metabolism of hormones, toxins, drugs and micronutrients. On a macronutrient level, it hinders the productions of proteins, undermines the synthesis of glucose from protein, the storage of glucose as glycogen in the liver and disrupts the metabolism of fat. This leads to a high risk of infections, hepatic encephalopathy (accumulation of toxins in the brain) and malnutrition. While liver transplantation is a treatment option for end stage liver disease, with increasing waiting times for organ transplantation, nearly 17% of patients on the waiting list, die on an annual basis. In addition, many patients are not eligible for transplantation due to comorbidities,

substance abuse, mental illness, insufficient psychosocial support and overall physical condition. Anything keeping patients with liver disease in the best possible physical condition is therefore important. Nutrition plays an important role in doing this.

Chapter 1 an introduction is given of all the chapters in this thesis focussing on malnutrition in end stage liver disease. It provides a summary of the role of nutrition with an emphasis on patients with end stage liver disease.

Chapter 2 presents a more in-depth overview of the different types of malnutrition in patients with end stage liver disease and questions current axioms. We found that the standard definition of malnutrition in these patients, protein energy malnutrition, although a strong indicator of higher morbidity and mortality, is not useful. Protein energy malnutrition indicates an insufficiency of both energy and protein (true protein energy malnutrition) or an insufficiency of protein (protein malnutrition) with sufficient energy. It makes however no distinction between these two types of malnutrition and neglects (severe) overweight and combinations of (severe) overweight and protein malnutrition.

(Severe) overweight is a cause of liver disease. In patients with end stage liver disease, it leads to further fibrogenesis, further disruption of nutrient and hormone metabolism and additional liver cell death. It is therefore associated with a higher mortality risk in these patients. The combination of (severe) overweight and protein malnutrition is independently associated with the highest mortality risks. Even so, protein energy malnutrition is underdiagnosed in clinical practice and protein malnutrition, (severe) overweight or a combination of these are often not even recognised as types of malnutrition. The prevalences of these types of malnutrition are therefore unknown.

In this chapter, we also report that the prevalence of true protein energy malnutrition is very low (up to 8%). Up to 61% of patients are however (severely) overweight and protein malnutrition is found in up to 51% of patients with end stage liver disease. The combination of both protein malnutrition and (severe) overweight in cirrhotics was found in up to 71%. These reported prevalences overlap greatly due to the current lack of clear markers of these different types of malnutrition.

As a step towards improved recognition of the different types and combinations of malnutrition, we proposed a differentiation in the definition. This definition is based on body protein and ectopic fat mass (fat where it does not belong). Protein mass and ectopic fat mass are independent risk factors in cirrhotic patients (as well as in the general population). For now, only an expensive and burdensome CT or MRI scan can measures protein and ectopic fat mass correctly. Whether these markers purely indicate malnutrition or are more general markers of the severity of disease is still uncertain but they are strong indicators of risks and can be improved by nutritional intervention. Protein mass an ectopic fat mass as measured with a CT or MRI scan, as well as the markers discussed below, are indicators of health risks that can be improved with nutritional interventions.

We have shown that hand grip strength, a marker of protein malnutrition, is an independent predictor of complications in cirrhosis (3). The combination of hand grip strength with BMI and waist-to-hip ratio can diagnose all types of malnutrition on a macronutrient level, at least in those without fluid retention. In patients with fluid retention, BMI corrected for estimated fluid retention (after validation in outpatients) combined with hand grip strength allows diagnosing almost all types of malnutrition in a clinical setting. It cannot differentiate between protein malnutrition and protein malnutrition with normal weight obesity (normal weight based on BMI but with a body fat percentage corresponding with obesity (men > 25%, women > 30% body fat)). There is an urgent need for markers of measuring the presence of ectopic fat that will make this differentiation possible as rates of obesity, but especially normal weight obesity and visceral fat, are already high and rising.
Including the correct assessment of the nutritional status into scoring systems of the mortality risk of end stage liver disease (Child Pugh and MELD score) may therefore increase their sensitivity and specificity, though further research is needed.

Current nutritional guidelines do need to be updated urgently as they focus only on true protein energy malnutrition, calling for both energy and protein enrichment. This is accurate in only up to 8% of patients. These guidelines do not differentiate between the different types of malnutrition in cirrhosis and ignore (severe) overweight. Following these guidelines may actually exacerbate liver disease in up to 61% of cirrhotics; those with an already high body fat mass. In these patients, energy enrichment may lead to even more inflammation and fibrogenesis, further disruption of nutrient and hormone metabolism and liver cell death. Possibly, this is one of the reasons why there is little evidence that standard nutritional advice is effective in these patients. Recent studies have demonstrated that specific nutritional interventions may indeed be effective in patients with protein malnutrition, (severe) overweight or both (4), and will prevent macronutrient malnutrition (5, 6).

For now, routine assessment of the nutritional status, preferably starting at the time of diagnosis of liver disease, is crucial. Nutritional advice based on the true nutritional status, established with the proposed markers, can be given. Loss of high risk ectopic fat mass, while preserving or increasing muscle mass and reducing insulin resistance should be the goal in most of these patients.

In **Chapter 3** we show that the prevalence of true protein energy malnutrition is also low among Dutch patients with end stage liver disease (5%). The prevalences of (severe) overweight, protein malnutrition and combinations of these are extremely high (up to 71% depending on the method of evaluation) among these patients. These high prevalences are seen even in early stages of end stage liver disease, indicating nutritional deficiency at relatively early stages of liver disease. We found a decrease of energy and protein intake with increasing Child Pugh class, which paralleled increasing hand grip insufficiency in cirrhotics. This coincided with a shift from protein to carbohydrate intake. Despite the decrease in energy intake, the BMI corrected for fluid retention did not differ between patients in the

three CP classes or between patients with sufficient or insufficient hand grip strength. Together, these findings suggest that inadequate protein intake could explain, at least partly, the high prevalence of malnutrition in patients with end stage liver disease. Quality of life was significantly lower in malnourished patients according to hand grip strength, a measure of protein deficiency.

In a 1-year follow up study we found that protein malnutrition was also associated with a higher mortality. More importantly, we demonstrated that malnutrition, measured with hand grip strength, indicating protein malnutrition, was an independent predictor of complications in cirrhosis. As we used current standard dietetic methods in this study, we were unable to assess the mortality risk of true obesity (fat percentage >25% in men or >30% in women) and the combination of true obesity and protein malnutrition. Recent studies, using CT scans for assessment of fat and protein mass, have shown that true obesity in combination with protein deficiency (here defined as sarcopenia) is associated with the highest mortality, especially when obesity is accompanied with myosteatosis (accumulation of fat in muscle mass) (**Fig. 4**) (7). The early diagnosis of these types of malnutrition is therefore also crucial in The Netherlands.

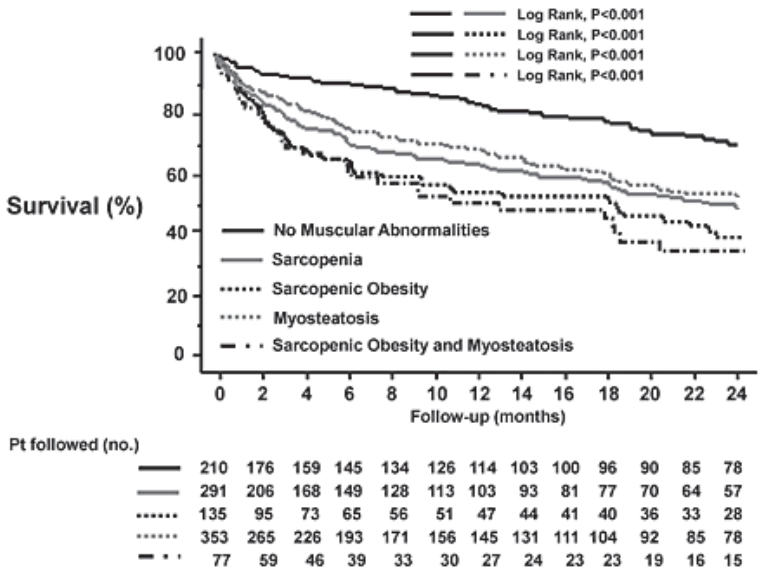

Figure 4. Effects of various forms of malnutrition on survival in cirrhotics (7). Reprinted with permission from author and publisher. Sarcopenia: protein malnutrition, Sacropenic obesity: protein malnutrition with high body fat mass, Myosteatosis: fat infiltration in the skeletal muscle.

Bacterial infection, possibly through increased intestinal permeability and bacterial overgrowth, is one of these serious and often fatal complications in liver cirrhosis (**Chapter 4**). We found that increased intestinal permeability, which is common in cirrhotics (8), was also significantly increased in Dutch cirrhotics. This may promote bacterial translocation and increase infection rate. Proton pump inhibitors (PPI), possibly enhancing bacterial overgrowth, may further increase this risk. In rats, bacterial overgrowth was much more common in jejunum treated with PPI or gastrectomy compared to non-treated rats. Even though PPI use was not an independent predictor of bacterial infection in humans, PPI users tended to experience more often infection than patients without PPI therapy after a 28-month follow-up. Stage of liver disease was the most important factor in the development of bacterial infections, with Child Pugh B or C patients having a 3-fold increased risk of bacterial infection compared to Child Pugh A patients. Furthermore, increasing age was an independent predictor of bacterial infections.

The aetiology of bacterial infections in cirrhotic patients is probably multifactorial. Intestinal permeability, gut flora and motility are changes in cirrhotic patients (8, 9). Furthermore, several abnormalities in the immune response have been described in cirrhotic patients (10, 11). Since these risk factors already exist in cirrhotic patients not on PPI therapy, use of PPIs may not have a significant additional effect on infection risk. Dietary fibre intake is extremely low in the general population, but particularly in cirrhotics (12). Fibres normally play a role in maintaining a healthy microbiota in the gut. If not available, the healthy microbiota will reduce and be replaced for less favourable bacteria, leading to immune dysregulation, inducing and enhancing inflammation already present in cirrhosis (13). As enterocytes derive up to 70% of their energy from short chain fatty acids produced by healthy microbiota from dietary fibre, insufficient fibre may lead to deterioration of these cells and their tight junctions, increasing gut permeability (14). As disturbances of gut microbiota are highly prevalent in patients with liver disease (15), this may be relevant, although future studies are needed.

Of importance, in our study PPIs were often prescribed in cirrhotic patients without an accepted indication. Although PPIs are generally regarded as drugs with a good safety profile, previous reports in non-cirrhotic patients indicate that PPI use is associated with an increased risk of infections (30). Therefore, routine use of acid suppressive drugs in cirrhotic patients is not recommended in the absence of an appropriate indication.

There are over 130-150 million patients with hepatitis C infection (HCV) worldwide (WHO 2015). Of these, 20% to 25% will develop liver cirrhosis. Antiquated antiviral treatment may cure approximately 50-80% of patients with HCV. However, severe side effects due to medication use often occur, including weight loss, digestive symptoms, and impaired quality of life. In **Chapter 5** we explored the beneficial effects of preventive nutritional support. In a randomized controlled trial, 53 HCV patients were allocated to ‘‘on demand’’ support (n = 26: nutritional intervention if weight loss >5%) or preventive support (n = 27: dietary advice plus energy- and protein-rich evening snack). Nutritional state (including validated Jamar Hand

Grip Strength), digestive symptoms, and quality of life were evaluated at baseline, and after 24 and 48 weeks of peginterferon alpha-2b and ribavirin treatment. The primary endpoint (weight loss at 24 weeks) was reached in 22 patients in both groups. Weight decreased markedly in the ''on demand'' group (decrease at 24 weeks: 5.4 kg or 6.9%, p <0.001), but not in the preventive group (decrease 0.3 kg or 0.3%, p = n.s.). Even more relevant was that the Jamar Hand Grip Strength deteriorated in the ''on demand'' group (from 40.3 ± 15.5 kg to 32.0 ± 13.1 kg, p <0.001) but not in the preventive group (from 40.7 ± 10.4 kg to 39.7 ± 8.9 kg, p = n.s.). These remarkable findings most probably are related to the increased ratio protein/carbohydrate intake and/or frequent intake of small meals in the preventive group. In conclusion, in contrast to ''on demand'' nutritional support, preventive nutritional support prevents weight loss and a catabolic state, with less side effects, improved digestive symptoms and quality of life during peginterferon alpha-2b plus ribavirin treatment for HCV.

In clinical practice, dose reductions of ribavirin and PEG interferon are often applied to improve quality of life and avoid sick-leave, which potentially compromise SVR rates. Dose reduction is the least favourable option in any treatment. Preventing this with such a simple and inexpensive tool as nutritional support should be considered in these patients.

Since the publication of this study new treatment regiments without ribavirin and PEG interferon have been introduced. Whether these treatments exert the same detrimental effect on the nutritional status in HCV patients remains to be seen. To our knowledge, this is however the first study providing proof of concept that specific nutritional support can indeed prevent a catabolic state, reduce digestive symptoms and deterioration of quality of life, even during an arduous and long term treatment with antiviral therapy.

Presence of chronic HCV is associated with a significant negative impact on paid labour productivity, physical exercise and performance status with further deterioration during PEG-interferon containing therapy. In **Chapter 6** we investigated whether preventive nutritional support during antiviral treatment for HCV, preventing the catabolic state, could also affect paid labour productivity, physical exercise and performance status. In a randomized controlled trial, 53 patients with chronic HCV were allocated to ''on demand'' support (n = 26: nutritional intervention if weight loss > 5%) or preventive support (n = 27: regular dietary advice plus energy- and protein-rich evening snack) during PEG-interferon containing therapy. At baseline, 46% of patients performed paid labour and 62% performed varying degrees of physical exercise. Furthermore, most patients could perform normal activity with only minor symptoms of disease (mean Karnofsky performance score: 94). Decreases of paid labour productivity (—21% vs. —70%, P = 0.003), physical exercise activity (—43% vs. —87%, P = 0.005) and Karnofsky performance scores (—12% vs. —24%, P < 0.001) were significantly less in the preventive than in the ''on demand'' group after 24 weeks of treatment. The effects of preventive nutritional support were even more pronounced after 48 weeks. Our main conclusion was that preventive nutritional support markedly ameliorates a decrease of paid labour productivity, physical exercise and performance status during PEG-interferon-containing treatment for chronic hepatitis C. The potential underlying mechanisms for the

beneficial effects may be an improved nutritional state, less digestive symptoms, fewer side effects and higher quality of life, as demonstrated previously (5). In the ‘‘on demand’’ group of our RCT, there was a trend towards a higher loss of paid labour productivity after 24 weeks of treatment in patients who performed blue collar labour at baseline than in those with white collar labour. Preventive nutritional support during antiviral therapy and its beneficial effect on paid labour productivity may theoretically be cost-effective.

In this thesis, the high prevalence of malnutrition in patients with end stage liver disease is described. Most patients are not protein and energy deficient but are (severely) overweight or both protein deficient and (severely) overweight. These latter types of malnutrition go largely undiagnosed due to current insufficient diagnostic tools but do lead to further deterioration of function of the already diseased liver and pose extreme health risks in general. Both the high prevalence of malnutrition and lack of diagnostic tools are not narrowed down to patients with liver disease. They may apply to any patient with any disease, if (severely) overweight. Specific nutritional advice is possible only after a correct assessment of the nutritional status. We provide proof of concept that positively influencing the nutritional status, purely with specific nutrition, is possible during long and arduous antiviral therapy.

Main findings and future perspectives

IIn this thesis, we investigate the nutritional status and the preservation of this in patients with liver disease. Our main findings are:

- The general term protein energy malnutrition is not useful as true protein energy malnutrition, which is the interpretation as formulated by NESPEN, is rare in these patients.
- Protein malnutrition, severe overweight and especially combinations of these are high risk types of malnutrition and are far more prevalent worldwide and in The Netherlands, and are seen even in early stages of end stage liver disease.
- Jamar Hand grip strength independently predicts the occurrence of complications is cirrhotics.
- Quality of life is significantly lower in malnourished cirrhotic patients according to hand grip strength.
- The decrease of energy and protein intake with increasing Child Pugh class and in hand grip insufficiency seen in cirrhotics coincides with a shift from protein to carbohydrate intake. Despite the decrease in energy intake, the BMIc is not different between patients in the three Child Pugh classes, or between patients with sufficient or insufficient hand grip strength. Together, these findings suggest that inadequate protein intake and an excess in carbohydrate intake may explain, at least partly, the high prevalence of malnutrition in patients with end stage liver disease.
- (Severe) overweight, especially ectopic fat, in patients with end stage liver disease enhances disease to further inflammation and fibrogenesis, disruption of nutrient and hormone metabolism and liver cell death.
- Cirrhotic patients with protein malnutrition, (severe) obesity or a combination of these (up to 71% of cirrhotics) are at the highest health risk and go undiagnosed for now as currently used diagnostic tools cannot identify these types of malnutrition.
- For patients without fluid retention, we propose a combination of simple and cheap diagnostic markers, namely BMI, hand grip strength and waist-to-hip ratio.
- For patients with fluid retention we propose a combination of simple and cheap diagnostic markers, namely BMI corrected for fluid retention and hand grip strength. However, marker for ectopic fat is needed for these patients.
- Current nutritional guidelines need to be updated as they only focus on true protein energy malnutrition and propose treating this with energy and protein enrichment present in only up to 8%.
- Loss of high risk ectopic fat mass, while preserving or increasing muscle mass and reducing insulin resistance (also with exercise) may be the goal of nutritional support in most patients.

- The health risks associated with malnutrition are high and prevention of deterioration of the nutritional status is easier than treating it. Correct and routine assessment of the nutritional status including the ratio protein/carbohydrate intake, preferably starting at the time of diagnosis of liver disease, may therefore be crucial.
- We provide proof of concept that preventive nutritional support can preserve the nutritional status, including handgrip strength, even during a long and arduous peginterferon-containing treatment for chronic hepatitis C. Preventive nutritional support improved digestive symptoms and quality of life and reduced side effects.
- Preventive nutritional support markedly ameliorates a decrease of paid labour productivity, physical exercise and performance status during HCV antiviral therapy. The potential underlying mechanisms for the beneficial effects may be an improved nutritional state and better quality of life.
- Nutritional therapy is not only cost effective (with costs of 660 euro per patient), it may reduce costs due to loss of paid labour productivity with 49%. Based on average incomes in 2016, this may reduce costs with 9000 euro during 24 weeks of treatment and 18,000 euro during 48 weeks of treatment.

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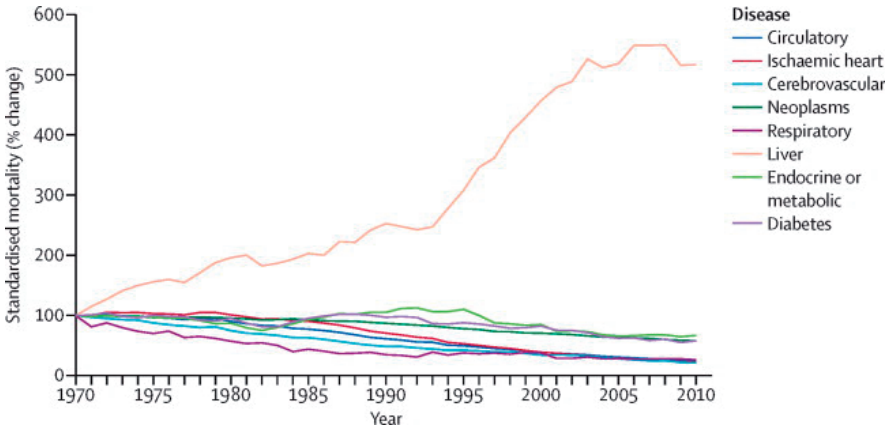
7

Chapter 8

Summary in Dutch
Samenvatting in het Nederlands

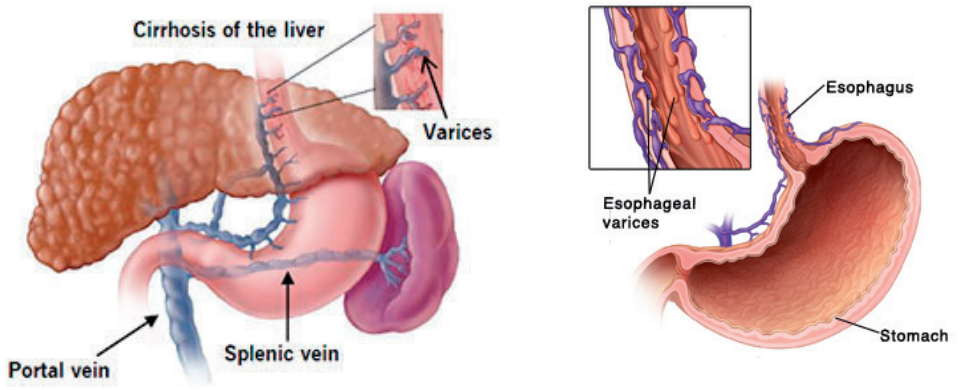
Leverziekten komen veel voor. Sterftecijfers van veel andere aandoeningen zoals hart- en vaatziekten en vele vormen van kanker zijn, dankzij grote investeringen in de zorg, de afgelopen decennia sterk gedaald. De sterfte ten gevolge van leverziekten is echter sterk gestegen, in Groot-Brittannië bijvoorbeeld met ruim 400% sinds 1970 (Fig. 1). Bij jonge patiënten met leverziekten is dit zelfs met 500% gestegen (1).



Figuur 1. **Gestandaardiseerde sterftecijfers (Groot-Brittannië)**

Data genormaliseerd naar 100% in 1970. Hieruit werden volgende trends uitgezet met behulp van de software 'Statistical Package for the Social Sciences'. De data zijn afkomstig van de WHO-HFA database en geanalyseerd door Nick Sheron (September, 2013). Herdrukt met toestemming van de auteur en de uitgever.

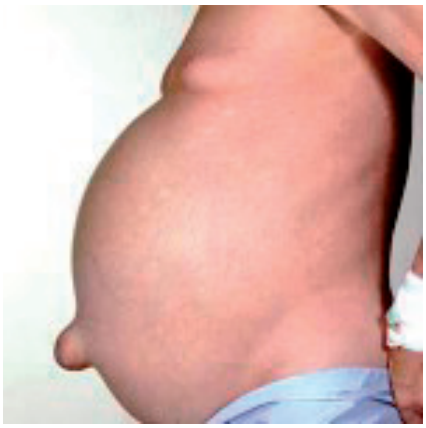
Levercirrose is het eindstadium van leverziekte bij patiënten met chronische progressieve vormen van leverziekten. Chronische progressieve leverziekte heeft veel verschillende oorzaken. Alcoholgebruik, chronische hepatitis C-infectie en niet-alcoholische leververvetting zijn hiervan de meest voorkomende. Meestal is sprake van een langzame progressie van de ziekte waarbij ontstoken en vaak ook steatotische (vervette) levercellen op den duur vervangen worden door littekenweefsel. Dit proces heet fibrose en deze verlittekening verstoort de doorbloeding van de lever. Hierdoor stijgt de intrahepatische weerstand en ontstaat portale hypertensie. Klinische symptomen van leverfalen worden gevonden wanneer meer dan 80-90% van de levercellen verwoest zijn door dit proces (2). Portale hypertensie veroorzaakt de vorming van varices (spataderen) in de slokdarm. Deze kunnen barsten en gaan bloeden (Fig. 2).



Figuur 2. Hoe leverziekte leidt tot bloedende varices

De verhoogde bloeddruk in het portale veneuze stelsel stuwt het bloed naar de omliggende bloedvaten, waaronder de bloedvaten rond de slokdarm, die hierdoor opzwellen. Deze vergrote aderen, varices genoemd, kunnen gaan bloeden. http://my.clevelandclinic.org/services/head-neck/diseases-conditions/hic-esophageal-varices en https://www.fairview.org/HealthLibrary/Article/40442. Herdrukt met toestemming.

Portale hypertensie veroorzaakt ook een verslechtering van de nierfunctie met water- en zoutretentie wat leidt tot oedeem en ascites (Fig. 3, vochtophoping in de buikholte) en een verhoogd hartminuutvolume.



Figuur 3. Ascites, of wel vochtophoping in de buikholte, is een veel voorkomende complicatie van levercirrose. Ascites ontstaat wanneer het functioneren van de lever begint af te nemen. Minder zichtbare ophoping van vocht begint vaak al gedurende eerdere stadia van leverziekten waardoor markers van ondervoeding dan al onbetrouwbaar zijn. Herdrukt met toestemming.

Fibrose verstoort ook de vele functies (meer dan 500) van de lever zelf. Het verstoort het metabolisme van hormonen, toxines, medicijnen en micronutriënten. Op macronutriëntniveau belemmert fibrose de productie van eiwitten en het metabolisme van vetten. Daarnaast ondermijnt fibrose de synthese van glucose uit eiwit en de opslag van

glucose als glycogeen in de lever. Dit leidt tot een verhoogd risico op infecties, hepatische encefalopathie (stapeling van toxines in de hersenen) en ondervoeding.

Levertransplantatie is een optie wanneer er sprake is van levercirrose. Echter, de wachttijden voor orgaantransplantatie worden steeds langer en jaarlijks sterft 17% van patiënten op de wachtlijst. Los daarvan komen veel patiënten niet in aanmerking voor transplantatie vanwege comorbiditeiten, verslavingen, psychische aandoeningen, onvoldoende psychosociale steun of onvoldoende lichamelijke conditie. Alle maatregelen die een patiënt met leverziekte in de meest optimale conditie kunnen houden zijn dan ook essentieel. Voeding speelt hierbij een belangrijke rol.

Hoofdstuk 1 is een introductie van alle hoofdstukken in dit proefschrift betreffende ondervoeding bij levercirrose. Het geeft een samenvatting van de rol van voeding in het algemeen en bij patiënten met leverziekten in het bijzonder.

In **Hoofdstuk 2** geven wij een uitvoeriger overzicht van alle voorkomende vormen van ondervoeding bij patiënten met levercirrose en stelden wij de huidige voedingsadviezen voor leverpatiënten ter discussie. Wij concludeerden dat de standaarddefinitie van ondervoeding bij deze patiënten, meer specifiek eiwitenergie-ondervoeding, niet goed bruikbaar is. Eiwitenergie-ondervoeding doelt op of op een tekort aan zowel energie als eiwit (werkelijke eiwitenergie-ondervoeding) of een tekort aan eiwit met voldoende energie (eiwitondervoeding). De standaarddefinitie onderscheidt deze twee vormen van ondervoeding echter niet. Daarnaast houdt deze definitie geen rekening met de mogelijkheid van (ernstig) overgewicht of de combinatie van (ernstig) overgewicht met eiwitondervoeding.

(Ernstig) overgewicht is op zich een oorzaak van leverziekte. Bij patiënten met levercirrose leidt (ernstig) overgewicht tot toename van reeds aanwezige fibrogenese (vorming van littekenweefsel) en verstoringen in het metabolisme van voedingsstoffen en hormonen. Ook leidt dit tot additionele sterfte van levercellen. (Ernstig) overgewicht is daardoor geassocieerd met een hoger mortaliteitsrisico bij deze patiënten. De combinatie van (ernstig) overgewicht én eiwitondervoeding is onafhankelijk geassocieerd met het hoogste mortaliteitsrisico. Toch wordt eiwitondervoeding zelden gediagnostiseerd in de kliniek. Eiwitondervoeding en (ernstig) overgewicht of de combinatie daarvan worden vaak helemaal niet herkend als vormen van ondervoeding. De prevalentie van deze vormen van ondervoeding is dan ook onbekend.

Uit literatuuronderzoek bleek dat de prevalentie van werkelijke eiwitenergie-ondervoeding heel laag was (maximaal 8%). Echter, 61% van de patiënten met levercirrose had (ernstig) overgewicht. Eiwitondervoeding werd gevonden in tot wel 51% van deze patiënten. De combinatie van zowel eiwitondervoeding als (ernstig) overgewicht werd gevonden in maximaal 71% van cirrotische patiënten. Wegens gebrek aan goede parameters overlapten de gerapporteerde prevalenties sterk.

Ter bevordering van de herkenning van de verschillende vormen van ondervoeding en combinaties van vormen van ondervoeding stellen wij een differentiatie in de definitie

van ondervoeding voor. Deze definitie is gebaseerd op de hoeveelheid lichaamseiwit en ectopisch lichaamsvet (vet op plaatsen waar het niet hoort, bijvoorbeeld in organen en spieren), maar dient nog gevalideerd te worden. De hoeveelheid lichaamseiwit en ectopisch lichaamsvet vormen beide onafhankelijke risicofactoren bij patiënten met levercirrose (net als onder de algemene bevolking). Beide zijn momenteel alleen correct te bepalen met een dure en belastende CT- of MRI-scan. Of deze parameters daadwerkelijk de voedingsstatus diagnosticeren of tezamen een meer algemene maat van de ernst van ziekte zijn, is nog onduidelijk. Wel zijn zowel de CT- als MRI-scan als de hieronder besproken parameters sterke indicatoren voor gezondheidsrisico's die aanzienlijk verlaagd kunnen worden met behulp van voedingsinterventies.

Wij toonden aan dat ook de handknijpkracht, een parameter voor eiwitondervoeding gemeten met de Jamar handdynamometer, een onafhankelijke voorspeller van complicaties is bij patiënten met levercirrose (3). De middel-heupratio is een maat voor ectopisch vet en de daarmee gepaard gaande gezondheidsrisico's. Met behulp van de combinatie van de handknijpkracht, de middel-heupratio en de BMI (goedkopere, eenvoudigere en minder belastende onderzoeksinstrumenten) kunnen alle vormen van ondervoeding op macronutriëntniveau gediagnostiseerd worden, behalve wanneer sprake is van vochtretentie. Dit komt frequent voor bij patiënten met levercirrose. Bij vochtretentie blijkt de BMI gecorrigeerd voor de geschatte hoeveelheid vocht in combinatie met de handknijpkracht uitkomst te kunnen bieden. Alleen het onderscheid tussen pure eiwitondervoeding of eiwitondervoeding gecombineerd met ectopische vervetting bij normale BMI ('normal weight obesity') kan dan nog niet gemaakt worden bij patiënten met vochtretentie. Er is dan ook dringend behoefte aan een parameter voor ectopisch vet waarmee dit onderscheid wel gemaakt kan worden: de prevalenties van obesitas, maar vooral van 'normal weight obesity' en ectopische vervetting zijn namelijk hoog en blijven toenemen.

Het toevoegen van een correct bepaalde voedingsstatus aan de scoringssystemen die gebruikt worden om het sterfterisico van patiënten met levercirrose te classificeren (Child Pugh klasse en MELD score) verhoogt mogelijk de sensitiviteit en specificiteit van deze systemen. Verder onderzoek is hier echter voor nodig.

Ook de huidige voedingsrichtlijnen dienen te worden herzien. Deze richtlijnen zijn alleen gericht op het herstel van werkelijke eiwitenergie-ondervoeding waarbij enkel zowel eiwit- als energieverrijking wordt geadviseerd. Dit advies is echter geschikt voor slechts maximaal 8% van de patiënten met levercirrose. Deze richtlijnen maken geen onderscheid tussen verschillende andere vormen van ondervoeding en negeren het bestaan van (ernstig) overgewicht. Het volgen van het advies uit deze richtlijnen versterkt mogelijk de ernst van leverziekte bij tot wel 61% van patiënten (die levercirrosepatiënten die ook een te hoog vetpercentage hebben). Eiwit- en energieverrijking kan bij deze patiënten leiden tot een nog hogere mate van ontsteking en fibrose, verdere verstoring van het metabolisme van nutriënten en hormonen, en leverceldood. Dit is mogelijk een van de redenen waarom standaardvoedingsadvies weinig of niet effectief is bij patiënten met levercirrose. Recente

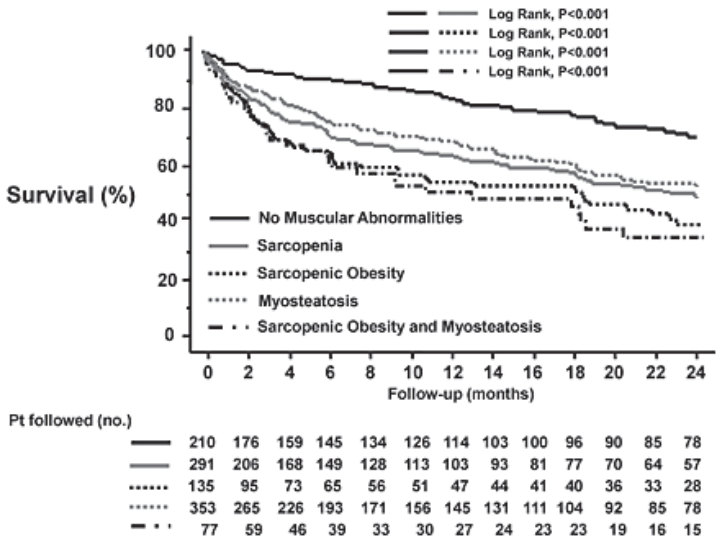
studies tonen aan dat individuele, op de patiënt toegesneden voedingsinterventies wel werken (4). Ook is, mede door ons, aangetoond dat ondervoeding met specifiek voedingsadvies kan worden voorkomen (5, 6).

Duidelijk is dat het routinematig correct bepalen van de voedingsstatus (liefst direct na de diagnose) essentieel is bij patiënten met levercirrose. Specifieke voedingsadviezen, gebaseerd op deze bepalingen kunnen dan worden gegeven. De preventie van ectopische vetopslag of het verminderen daarvan, met behoud of toename van spiermassa en het reduceren van insulineresistentie dienen de belangrijkste doelen te zijn bij de meeste patiënten.

In **Hoofdstuk 3** toonden we aan dat de prevalentie van werkelijke eiwitenergie-ondervoeding ook laag is bij patiënten met levercirrose in Nederland (5%). De prevalenties van (ernstig) overgewicht, eiwitondervoeding en de combinaties hiervan bij deze patiënten zijn echter ook hier hoog (25%-71%, afhankelijk van de meetmethode). Deze hoge prevalenties werden al gevonden in vroege stadia van levercirrose. Dit betekent dat ondervoeding al aanwezig is in vroegere stadia van leverziekten voorafgaande aan cirrose. De inname van energie en eiwit nam af bij een toename in ernst van levercirrose (Child Pugh klasse). Tegelijkertijd nam de handknijpkracht (een maat voor eiwitondervoeding) af. Deze afname in handknijpkracht ging gepaard met een verschuiving van inname van eiwit naar koolhydraten. Ondanks de daling in energie-inname verschilde de BMI niet tussen de patiënten in de verschillende Child Pugh klassen of tussen de patiënten met een voldoende of onvoldoende grote handknijpkracht. De BMI op zich geeft dan ook geen inzicht in de voedingsstatus. Tezamen suggereren deze bevindingen dat een onvoldoende inname van eiwit, tenminste gedeeltelijk, de hoge prevalentie van ernstige ondervoeding bij patiënten met levercirrose kan verklaren. Daarnaast was de kwaliteit van leven sterk verminderd bij patiënten met een onvoldoende grote handknijpkracht, een maat voor eiwitondervoeding.

In een studie met gemiddeld 1 jaar follow-up toonden wij aan dat er een relatie is tussen eiwitondervoeding en een hogere mortaliteit. Ondervoeding, gemeten met de handknijpkracht, was een onafhankelijke voorspeller van complicaties bij patiënten met levercirrose. Omdat in deze studie gebruik gemaakt is van de huidige standaard antropometrische parameters was het niet mogelijk het sterfterisico van echte obesitas (vetpercentage van > 25% bij mannen en > 30% in vrouwen) en de combinatie van echte obesitas en eiwitondervoeding te bepalen.

Recente studies, waarin gebruik gemaakt werd van CT-scans voor het bepalen van de vet- en eiwitmassa, laten zien dat echte obesitas gecombineerd met eiwitondervoeding (sarcopenie) geassocieerd is met de hoogste mortaliteit. Met name wanneer dit gepaard ging met myosteatose (stapeling van vet in de spiermassa) (**Figuur 4**) (7).



Figuur 4. De effecten van de verschillende vormen van ondervoeding op overleving bij patiënten met levercirrose (7). Geprint met toestemming van de auteur en uitgever. Sarcopenia: eiwitondervoeding, Sacropenic obesity: eiwitondervoeding in combinatie met een te hoog vetpercentage, Myosteatosis: infiltratie van vet in de spieren.

Bacteriële infecties, mogelijk veroorzaakt door een toename in de intestinale permeabiliteit (doorlaatbaarheid van de darmwand) en bacteriële overgroei, vormen een van de meest serieuze en vaak fatale complicaties bij patiënten met levercirrose (**Hoofdstuk 4**). Wij toonden aan dat de intestinale permeabiliteit ook bij Nederlandse patiënten met levercirrose, net als elders in de wereld (8), significant verhoogd is. Mogelijk bevordert dit de bacteriële translocatie en daarmee de kans op infecties. Protonpomp remmers (proton pump inhibitors; PPI), die mogelijk de kans op bacteriële overgroei vergroten, kunnen dit risico versterken. Bacteriële overgroei kwam veel meer voor in het jejunum van ratten behandeld met PPI of gastrectomie dan in niet behandelde ratten. Patiënten met PPI-therapie bleken vaker infecties te hebben dan patiënten zonder PPI-therapie, al was PPI-gebruik geen onafhankelijke voorspeller van bacteriële infecties. Het stadium van leverziekte was de belangrijkste factor voor de ontwikkeling van bacteriële infecties, waarbij Child Pugh klasse B- of C-patiënten een drie maal zo hoog risico op het ontwikkelen van een bacteriële infectie hadden in vergelijking met Child Pugh klasse A-patiënten. Een hogere leeftijd was ook een onafhankelijke voorspeller van het ontstaan van bacteriële infecties.

De etiologie van bacteriële infecties bij patiënten met levercirrose is waarschijnlijk multifactorieel. De intestinale permeabiliteit, de darmflora en de motiliteit zijn allemaal veranderd bij patiënten met levercirrose (8, 9). Daarnaast zijn ook verschillende abnormale immuunreacties beschreven bij deze patiënten (10, 11). Gezien deze reeds bestaande risicofactoren bij patiënten met levercirrose zonder PPI-therapie heeft het gebruik van PPI's mogelijk geen significant additief effect op het infectierisico.

De inname van voedingsvezels is extreem laag in de algemene populatie en bij patiënten met levercirrose in het bijzonder (12). Vezels spelen een belangrijke rol bij het onderhouden van een gezond microbioom in de darm. Bij het ontbreken van deze vezels neemt het aantal zogenaamde gezonde micro-organismen af en worden deze vervangen door minder gunstige micro-organismen. Dit kan leiden tot ontregeling van het immuunsysteem en het ontstaan en versterken van ontstekingsprocessen die al aanwezig zijn bij patiënten met levercirrose (13). Tot wel 70% van de energie die enterocyten (cellen waaruit de darmwand is opgebouwd) verbruiken, is afkomstig van korteketenvetzuren geproduceerd door gezonde micro-organismen uit voedingsvezels. Inname van onvoldoende vezels leidt dan ook mogelijk tot een verslechtering van de conditie van deze cellen en hun onderlinge verbinding (tight junctions). Hierdoor zou een verhoogde permeabiliteit kunnen ontstaan (14). Dit is mogelijk relevant omdat verstoringen in het microbioom van patiënten met leverziekten veelvuldig voorkomen (15).

Belangrijk is dat in onze studie PPI's vaak werden voorgeschreven aan patiënten met levercirrose zonder een geaccepteerde indicatie hiervoor. Hoewel PPI's in het algemeen als medicatie met een goed veiligheidsprofiel worden beschouwd, blijkt uit eerder onderzoek bij patiënten zonder levercirrose dat PPI-gebruik geassocieerd is met een verhoogd risico op infecties (30). Het routinematig gebruik van maagzuurremmende medicatie bij patiënten met levercirrose wordt dan ook afgeraden wanneer er geen sprake is van een geaccepteerde indicatie hiervoor.

Wereldwijd zijn er meer dan 130 - 150 miljoen patiënten met een hepatitis C-infectie (WHO 2015). Hiervan zal 20% tot 25% levercirrose ontwikkelen. De eerste generatie antivirale therapie, gebaseerd op peginterferon en ribavirine, geneest ongeveer 50 tot 80% van patiënten met hepatitis C. De bijwerkingen van therapie met peginterferon en ribavirine, waaronder gewichtsverlies, spijsverteringsklachten en een afname van kwaliteit van leven, zijn echter ernstig en komen veelvuldig voor. In **Hoofdstuk 5** is onderzocht wat het effect is van preventieve voedingsondersteuning gedurende deze behandeling. In een gerandomiseerde, gecontroleerde studie werden 53 patiënten met hepatitis C-infectie gerandomiseerd tussen 'on demand'-voedingsondersteuning (n = 26: voedingsondersteuning bij gewichtsverlies >5%) of preventieve voedingsondersteuning (n = 27: voedingsadvies en een energie- en eiwitverrijkte avondsnack). De voedingsstatus (inclusief de gevalideerde handknijpkracht (Jamar)), spijsverteringsklachten en de kwaliteit van leven werden geëvalueerd voor aanvang en na de 24 en 48 weken durende behandeling met peginterferon α-2b en ribavirine. Het primaire eindpunt (24 weken behandeling) werd bereikt door 22 patiënten in beide groepen. Het lichaamsgewicht nam aanzienlijk af in de 'on demand'-groep (gewichtsafname na 24 weken: 5,4 kg ofwel 6,9%, p <0.001), maar niet in de groep met preventieve voedingsondersteuning (gewichtsafname 0,3 kg ofwel 0.3%, p = n.s.). De handknijpkracht verslechterde in de 'on demand'-groep (van 40,3 ± 15,5 kg naar 32,0 ± 13,1 kg, p <0.001) maar niet in de groep met preventieve voedingsondersteuning (van 40,7 ± 10,4 kg naar 39,7 ± 8,9 kg, p = n.s.). Deze bevindingen konden worden gerelateerd aan een toegenomen

ratio van ingenomen eiwit ten opzichte van koolhydraten in de groep met preventieve voedingsondersteuning. Preventieve voedingsondersteuning voorkomt dus gewichtsverlies en katabolisme (spierafbraak). Ook zorgt dit voor minder spijsverteringsklachten en andere bijwerkingen en leidt het tot een betere kwaliteit van leven tijdens de behandeling.

In de klinische praktijk werd vroeger vaak een reductie van de dosering van peginterferon en ribavirine toegepast om de kwaliteit van leven te verbeteren en ziekteverzuim te verlagen. Hiermee daalt echter de kans op het slagen van de behandeling. Het voorkomen hiervan met behulp van eenvoudige en goedkope preventieve voedingsondersteuning dient dan ook te worden overwogen bij deze patiënten.

Sinds de publicatie van dit onderzoek zijn nieuwe behandelmogelijkheden geïntroduceerd. Of deze behandelingen ook schadelijke effecten hebben op de voedingsstatus is nog niet bekend. Voor zover wij weten is onze studie echter de eerste waarin wordt aangetoond dat specifieke voedingsondersteuning daadwerkelijk katabolisme kan voorkomen en spijsverteringsklachten, bijwerkingen en de verslechtering van de kwaliteit van leven kan verminderen, zelfs tijdens langdurige en zware antivirale therapie met peginterferon en ribavirine.

De arbeidsproductiviteit, het vermogen tot fysieke activiteit en het participatieniveau (de 'Karnofsky-score') zijn reeds significant verlaagd bij patiënten met chronische hepatitis C. Gedurende antivirale therapie met peginterferon en ribavirine nemen die nog verder af. In **Hoofdstuk 6** werd onderzocht of het voorkomen van katabolisme met preventieve voedingsondersteuning ook een gunstig effect heeft op de arbeidsproductiviteit, fysieke activiteit en het participatieniveau. In een gerandomiseerde, gecontroleerde studie werden 53 patiënten met hepatitis C-infectie gerandomiseerd tussen 'on demand'-ondersteuning of preventieve voedingsondersteuning (zie hierboven). Bij aanvang verrichtte 46% van alle patiënten betaalde arbeid en 62% van de patiënten verrichtte enige vorm van fysieke activiteit. Het merendeel van de patiënten was in staat tot normale participatie met slechts minimale symptomen van ziekte (gemiddelde Karnofskyscore: 94). Na 24 weken behandeling waren de afnames van arbeidsproductiviteit (—21% vs. —70%, P = 0,003), fysieke activiteit (—43% vs. —87%, P = 0,005) en Karnofskyscores (—12% vs. —24%, P < 0,001) significant minder in de groep met preventieve voedingsondersteuning dan in de 'on demand'-groep. De effecten van preventieve voedingsondersteuning waren nog groter na 48 weken behandeling. Hieruit concludeerden wij dat preventieve voedingsondersteuning gedurende antivirale therapie met peginterferon en ribavirine de afname van arbeidsproductiviteit, fysieke activiteit en het participatieniveau drastisch vermindert. Mogelijke onderliggende oorzaken van dit positieve effect zijn het voorkomen van gewichtsverlies en katabolisme, minder spijsverteringsklachten en bijwerkingen, en een hogere kwaliteit van leven (5). In de 'on demand'-groep was, na 24 weken behandeling, een trend naar meer verlies van arbeidsproductiviteit zichtbaar bij patiënten die 'blue collar'-arbeid verrichtten dan bij patiënten die 'white collar'-arbeid verrichtten. Preventieve voedingsondersteuning gedurende antivirale therapie met het daarmee gepaard gaande positieve effect op de

arbeidsproductiviteit is wellicht kosteneffectief. Mogelijk kan preventief voedingsadvies de kosten van het verlies van arbeidsproductiviteit met circa 50% verlagen.

Bovenstaande maakt duidelijk dat de huidige standaard diagnostische hulpmiddelen voor het bepalen van de voedingsstatus niet geschikt zijn voor gebruik bij patiënten met levercirrose. Het overgrote deel van deze patiënten lijdt niet aan eiwitenergie-ondervoeding maar heeft (ernstig) overgewicht of eiwitondervoeding met of zonder (ernstig) overgewicht. De huidige hulpmiddelen diagnosticeren de laatstgenoemde vormen van ondervoeding niet. Deze vormen leiden echter wel tot een verdere verslechtering van de leverfunctie in de reeds zieke lever en vormen grote gezondheidsrisico's in het algemeen. Deze tekortkomingen in de diagnostiek en de genoemde gezondheidsrisico's beperken zich zeer waarschijnlijk niet tot patiënten met levercirrose, maar zijn mogelijk ook van toepassing op patiënten met andere aandoeningen wanneer die gepaard gaan met (ernstig) overgewicht, zeker als ook sprake is van eiwitondervoeding. Pas na een correcte bepaling van de voedingsstatus is specifiek voedingsadvies mogelijk. Wij leveren 'proof of concept' dat het mogelijk is de voedingsstatus enkel met specifiek voedingsadvies positief te beïnvloeden, zelfs gedurende lange en zware peginterferon- en ribavirinebevattende antivirale therapie bij patiënten met hepatitis C.

Belangrijkste conclusies van dit proefschrift en aanbevelingen voor de toekomst

Dit proefschrift beschrijft onderzoek naar de voedingsstatus en het behoud daarvan bij patiënten met leverziekten. Onze belangrijkste conclusies zijn:

- De algemene term eiwitenergie-ondervoeding is niet bruikbaar omdat werkelijke eiwitenergie-ondervoeding, zoals geformuleerd door NESPEN, zeldzaam is bij patiënten met levercirrose.
- Eiwitondervoeding, (ernstig) overgewicht en vooral combinaties daarvan zijn vormen van ondervoeding met een zeer hoog gezondheidsrisico die, zowel wereldwijd als in Nederland, veel vaker en zelfs al in de vroege stadia van levercirrose voorkomen.
- Handknijpkracht is een onafhankelijke voorspeller van complicaties bij patiënten met levercirrose.
- De kwaliteit van leven was significant lager bij patiënten met levercirrose die ondervoed waren volgens de handknijpkracht.
- De afname in handknijpkracht bij patiënten met levercirrose ging gepaard met een verschuiving van inname van eiwit naar koolhydraten. Ondanks de daling in energie-inname verschilde de BMI niet tussen de patiënten in de verschillende Child Pugh klassen of tussen de patiënten met een voldoende of onvoldoende grote handknijpkracht. De BMI op zich geeft dan ook geen inzicht in de voedingsstatus. Tezamen suggereren deze bevindingen dat een onvoldoende inname van eiwit, tenminste gedeeltelijk, de hoge prevalentie van ernstige ondervoeding bij patiënten met levercirrose kan verklaren.
- Bij patiënten met levercirrose leidt (ernstig) overgewicht en vooral ectopische vervetting tot een verslechtering van leverziekte. Deze vervetting versterkt reeds aanwezige ontstekingsprocessen en fibrogenese, verstoort het nutriënt- en hormoonmetabolisme en veroorzaakt leverceldood.
- Patiënten met levercirrose en eiwitondervoeding, (ernstig) overgewicht of een combinatie hiervan (tot wel 71% van de patiënten) staan bloot aan de grootste gezondheidsrisico's. Dit wordt echter zelden gediagnostiseerd omdat de huidige standaard diagnostische hulpmiddelen deze vormen van ondervoeding niet kunnen diagnosticeren.
- Voor de diagnose van ondervoeding bij patiënten zonder vochtretentie stellen wij het gebruik van simpele en goedkope parameters voor; de BMI, handknijpkracht en de middel-heupratio.
- Voor de diagnose van ondervoeding bij patiënten met vochtretentie stellen wij het gebruik van de volgende parameters voor; de BMI gecorrigeerd voor vochtretentie en de handknijpkracht.
- De huidige voedingsrichtlijnen voor patiënten met levercirrose en ondervoeding dienen dringend te worden herzien omdat deze zich enkel richten op werkelijke eiwitenergie-ondervoeding.

- Het voornaamste doel van voedingsondersteuning bij het merendeel van patiënten met levercirrose is mogelijk het verlagen van de ectopische vetmassa terwijl de spiermassa behouden blijft of toeneemt en insulineresistentie (ook met behulp van fysieke activiteit) afneemt.
- De gezondheidsrisico's geassocieerd met ondervoeding zijn groot en het voorkomen van een verslechtering van de voedingsstatus is eenvoudiger dan het behandelen hiervan. Correcte en routinematige beoordeling van de voedingsstatus inclusief de ratio van inname van eiwit versus koolhydraten, bij voorkeur direct na diagnose van leverziekte, is dan ook cruciaal.
- Wij leveren 'proof of concept' dat preventieve voedingsondersteuning de voedingsstatus, inclusief de handknijpkracht, in stand kan houden, zelfs gedurende lange en zware peginterferon en ribavirine bevattende therapie. Ook verminderden hiermee spijsverteringsklachten en het aantal bijwerkingen en verbeterde de kwaliteit van leven.
- Preventieve voedingsondersteuning verlaagt het verlies aan arbeidsproductiviteit aanmerkelijk. Potentiele achterliggende mechanismen hiervan zijn de betere voedingsstatus en hogere kwaliteit van leven.
- Voedingsondersteuning is niet alleen kosteneffectief (660 euro per patiënt). Het reduceert de kosten die gepaard gaan met verlies aan arbeidsproductiviteit mogelijk circa 50%. Uitgaande van een gemiddeld inkomen in 2017 kan dit leiden tot een besparing van 9000 euro gedurende een behandeling van 24 weken en 18.000 euro gedurende een behandeling van 48 weken.

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Ellen Huisman
Lochem, augustus 2017

List of abbreviations

BCM	body cell mass
BMI	body mass index
BMIc	body mass index corrected for fluid retention
CP class	Child Pugh class
CT	computer tomography
ESPEN	European Society for Clinical Nutrition and Metabolism
GL	glycaemic load
H2RAs	H2 receptor antagonists
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HGS	hand grip strength
HOMA	homeostasis model assessment
KPS	Karnofsky performance status
MAC	mid arm circumference
MAMC	mid arm muscle circumference
MH	mental health
MM	micronutrient malnutrition
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatotic hepatitis
NWO	normal weight obesity
PEG	polyethylene glycol
PEM	protein energy malnutrition
PH	physical health
PM	protein malnutrition
PPI	proton pomp inhibitors
SBP	spontaneous bacterial peritonitis
SF-36	Medical Outcomes Study 36-item Short-Form General Health Survey
SGA	subjective global assessment
(S)O	(severe) overweight
TSF	triceps skin fold thickness

List of publications

1: Huisman EJ, Malnutrition in end stage liver disease; is it time to differentiate the diagnostics? In press.

2: Huisman EJ, van Meer S, van Hoek B, van Soest H, van Nieuwkerk KM, Arends JE, Siersema PD, van Erpecum KJ. Effects of preventive versus ''on-demand'' nutritional support on paid labour productivity, physical exercise and performance status during PEG-interferon-containing treatment for hepatitis C. Clin Res Hep Gastr 2016 Apr;40(2):221-9.

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Curriculum vitae

Ellen Julia Huisman werd geboren op 6 januari 1971 in Geldrop. In 1992 rondde zij het atheneum af op het Strabrecht College in Geldrop, waarna zij Biomedische Wetenschappen ging studeren aan de Universiteit Leiden. Aan het begin van het tweede studiejaar (1993) raakte zij betrokken bij een auto-ongeval waardoor zij lange tijd moest revalideren. Tijdens deze revalidatieperiode heeft zij, in samenwerking met de Universiteit Leiden, een vrij doctoraal Biomedische Wetenschappen mogen opstellen waardoor vervolg van de studie uiteindelijk in 1999 mogelijk werd.

Vervolgens startte zij in 2006 met de opleiding Voeding en Dietethiek (aangepast) aan de Haagse Hogeschool. Deze studie rondde zij in 2009 af. Haar eerste stages voor beide opleidingen liep zij in het Leids Universitair Medisch Centrum op de afdeling Maag-, Darm-, Leverziekten onder leiding van diëtiste Anneke Donker (voor de opleiding Voeding en Dietethiek) en professor dr. A. Masclee (voor de opleiding Biomedische Wetenschappen). Deze laatstgenoemde stage resulteerde in een eerste wetenschappelijke publicatie.

Onder leiding van dr. K.J. van Erpecum en professor P.D. Siersema heeft Ellen haar tweede stage voor Biomedische Wetenschappen gelopen in het Universitair Medisch Centrum Utrecht. Hier onderzocht zij de voedingsstatus van patiënten met levercirrose. Ook deze stage resulteerde in een wetenschappelijke publicatie en was tevens het begin van het promotieonderzoek waarmee zij, na afronding van de studie Biomedische Wetenschappen in 2010 startte. Momenteel heeft zij haar eigen praktijk als diëtiste en is bezig met het opzetten van vervolgonderzoek naar onder andere specifieke voeding bij non alcoholic fatty liver disease.