Review paper

Forgettable in the care of liver cirrhosis: the unseen culprits of progression from bad to worse

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Abstract

Patients with liver cirrhosis constitute a critically ill and unique population, and their stability relies on a well-coordinated multidisciplinary team with a carefully structured plan. Overlooking any aspect of this plan can expedite disease progression, leading to severe complications. The lack of disease-specific nutritional guidance, the prevalent sedentary lifestyle among patients, and insufficient screening for hepatocellular carcinoma, oesophageal varices, sarcopaenia, minimal hepatic encephalopathy, and diabetes mellitus, along with fibrosis progression and cirrhosis decompensation, can add further complexities. Additionally, devaluing the impact of obesity in triggering liver cirrhosis can be disadvantageous. Prolonged and inappropriate use of proton pump inhibitors also poses a significant challenge with a wide range of complications. These often-unheeded aspects in the care of liver cirrhosis patients represents the unseen culprits of progression from bad to worse and warrant serious consideration.

Introduction

Patients with liver diseases endure significant suffering and look to hepatologists as their beacon of hope for relief. However, failure to adhere to internationally recommended care guidelines for liver cirrhosis can exacerbate the plight of individuals already battling with their diseased livers. This article sheds light on the often-devalued aspects of caring for liver cirrhosis patients.

Nutritional considerations

Malnutrition represents a substantial burden in patients with liver cirrhosis, with a prevalence of 20% in compensated cirrhosis and over 60% in decompensated cases [1]. Malnutrition in cirrhosis stems from a combination of factors, including reduced oral intake due to issues like poor appetite, nausea, ascites, taste alterations, bland diets, medication side effects, diet restrictions, and continued alcohol consumption [2]. Additionally, cirrhosis can hinder nutrient utilisation through complications like fat malabsorption, bile acid deficiency, and the effects of portal hypertension, which may result in gastropathy and enteropathy, added to gastroparesis and autonomic dysfunction. The presence of bacterial overgrowth and the chronic use of lactulose further compound these challenges [2]. Alterations in carbohydrate and protein metabolism, such as the development of insulin resistance, increased gluconeogenesis, abnormal amino acid processing, and heightened protein catabolism, also contribute to malnutrition [2]. Furthermore, micronutrient deficiencies might add complexities to the condition [3]. These combined factors can lead to a state resembling starvation, characterised by reduced levels of glucose, protein, and lipids, intensifying the risk of malnutrition in cirrhotic individuals [3]. Malnutrition is closely linked to the progression to end-stage liver disease [2]. Consequently, patients with severe advanced chronic liver disease might suffer weakness, sarcopaenia, frailty, osteoporosis or even fractures, and recurrent infections among a long list of penalties of malnutrition [3]. If there is one factor that can genuinely alleviate the suffering of these patients and improve their conditions, it is nutritional assessment and correction [1]. The role of dietary adjustments in liver disorders is undeniable, as the liver plays a pivotal role in the metabolism of all dietary components (carbohydrates, fats, proteins) [3].

Dietary recommendations are a crucial component of guidelines for all liver disorders, whether acute or chronic [4]. Here, we discuss the commonest dietary considerations to be kept in mind when dealing with chronic liver disease patients.

Protein restriction in patients with liver cirrhosis

It is a common but misadvised practice among many physicians to restrict protein intake, principally out of fear of precipitating hepatic encephalopathy due to elevated ammonia levels. However, patients with chronic liver diseases typically require higher protein intake due to their elevated metabolic rate [5]. It is worth noting that restricting protein has been found to have no impact on the recurrence of hepatic encephalopathy [6]. The American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Parenteral and Enteral Nutrition guidelines recommend no special alterations in dietary protein for patients with compensated cirrhosis, while those with decompensated cirrhosis should aim for a daily protein intake of 1.2–1.5 g/kg, and 0.6–0.8 g/kg if acute encephalopathy develops [6–8]. While some reports suggest that dairy or vegetable proteins may be better for patients with hepatic encephalopathy compared to animal proteins, no clear superiority has been established [8, 9]. Conversely, complete protein restriction is unwarranted and can lead to more complications, including infections and ascites, along with a severely diminished quality of life and increased short-term mortality [10]. Sarcopaenia, a significant factor affecting the quality of life in patients with chronic liver disease, is reported in approximately 70% of decompensated cirrhosis patients [11]. Among the various factors contributing to sarcopaenia in decompensated cirrhosis, protein restriction is a major factor [12, 13]. Therefore, adhering to justifiable protein intake, as recommended by international guidelines for patients with chronic liver disease, is crucial in mitigating the severe impacts on this patient population. These recommendations must be emphasised to all young physicians dealing with chronic liver disease patients. However, further research is needed to precisely define the role of protein in controlling and improving liver disease across all categories.

The importance of caloric dietary recommendations

Patients with decompensated liver disease face unique challenges due to the depletion of their glycogen stores, necessitating specific dietary adjustments. It is crucial to provide optimal daily energy intake, which should not fall below 35 kcal/kg of their actual body weight [6]. Daily meals should consist of 3 main components, supplemented by 3 snacks throughout the day (mid-morning, mid-afternoon, and late evening). To prevent morning hypoglycaemia, late-evening oral nutritional supplementation (ONS) emerges as a pivotal recommendation [14]. If followed correctly, these relatively simple guidelines have the potential to alleviate the suffering experienced by this severely afflicted patient group. Patients with decompensated liver disease must strictly avoid fasting for extended periods, whether as part of Islamic fasting, intermittent fasting, or due to anorexia. They should be explicitly instructed not to fast for more than a few hours.

Caloric deficiency can contribute to the widespread weakness and reduced quality of life observed in patients with chronic liver disease [15]. Nevertheless, further research is needed to explore the specific patterns of impairment associated with caloric deficiency in different categories of chronic liver diseases. Additionally, there is an unfulfilled need to investigate the impact of caloric control on diseased livers, particularly in cases of obesity and non-alcoholic fatty liver diseases, where low-carbohydrate diets may be essential but still present unmet challenges.

The role of fat in cirrhosis management

Fat restriction in patients with liver cirrhosis is a common but misguided practice that complicates the already challenging issue of malnutrition. The primary misconception stems from the altered fat metabolism within the diseased liver. Additionally, these patients often experience maldigestion due to a congested gastrointestinal tract and portal hypertensive gastropathy, further exacerbating their condition [16]. The unappealing nature of fat-free diets can contribute to anorexia and dysgeusia, which are commonly reported in patients with advanced liver cirrhosis [16].

While fat restriction is generally considered a healthy dietary choice, complete fat elimination, especially when combined with alleged salt restriction in cirrhosis patients, can lead to reduced nutritional intake. Furthermore, it can aggressively worsen deficiencies in fat-soluble vitamins. Fats should not be restricted outright in this unique patient population; they should instead be recognised as a fundamental nutritional component essential for vital bodily functions necessary for a healthier, longer life. Achieving a balanced fat intake may pose a challenge, particularly in patients with dyslipidaemias associated with non-alcoholic fatty liver disease (NAFLD). Further research is imperative to fully comprehend and strike the delicate balance required for optimal management of this critical cohort.

Re-evaluating the role of dietary salt in liver cirrhosis

The management of dietary salt intake in patients with liver cirrhosis is a nuanced topic that balances between unjustifiable restriction and unrestricted allowances. In general, salt intake should be limited in all individuals due to its well-documented adverse health effects. However, complete sodium (Na) restriction is not recommended for cirrhotic patients without ascites. This is primarily because strict Na restriction can render food unpalatable, potentially exacerbating malnutrition and its associated complications, including hyponatraemia, hypoalbuminaemia, renal failure, and hepatic encephalopathy. Most guidelines recommend salt restriction for cirrhotic patients with ascites but provide no specific recommendations for those without ascites [17].

In patients with decompensated cirrhosis, especially those with ascites, the daily allowable sodium intake should not exceed 6.5 g (equivalent to 87–113 mmol of sodium) [18]. This means that adding table salt to food is discouraged. However, salt restriction to control ascites remains a subject of debate, primarily due to concerns about malnutrition [17]. Malnutrition in cirrhotic patients is strongly associated with increased morbidity and mortality, as well as a diminished health-related quality of life [19]. Dietary sodium comes primarily from animal proteins, grains, and dairy products, which are essential nutritional components required for overall health. Studies have shown a clear link between sodium restriction in cirrhotic ascites patients and malnutrition, leading to reduced intake of various food groups, resulting in lower energy, total fat, saturated fat, protein, carbohydrate, and calcium intake [20]. Furthermore, sodium restriction may exacerbate the multifactorial anorexia experienced by cirrhotic patients [21].

The combination of salt restriction and diuretics, alongside pre-existing hyponatraemia in cirrhotic patients, can lead to symptomatic hyponatraemia, including symptoms such as nausea, vomiting, lethargy, and lassitude [22]. This can progress to acute hyponatraemia syndrome, hyponatraemic encephalopathy, and hepatorenal syndrome [23]. Additionally, low serum sodium levels can result in reduced renal blood flow, activation of the renin-angiotensin-aldosterone system (RAAS), increased ascites accumulation, and renal impairment [23].

However, only a limited number of studies have investigated the impact of salt restriction on ascites control. One notable study by Soulsby *et al.* in 2012 randomised cirrhotic patients with ascites into 2 groups, one with restricted sodium intake (4.2 g of NaCl) and the other without such restriction (8.8 g of NaCl). Surprisingly, the non-salt restriction group showed a significant reduction in ascites, improved nutritional status, and shorter hospital stays [20]. Another study by Gu *et al.* in 2012 also demonstrated the superiority of a 10-day unrestricted sodium group over a restricted group in terms of ascites improvement, diuresis, renal blood flow, total caloric intake, and serum albumin, with fewer associated complications [23]. In the same year, Sorrentino *et al.* (2012) reported on the impact of sodium restriction on ascites re-accumulation after 1 year of paracentesis. Impressively, the sodium-restricted group required more frequent paracentesis and had higher mortality rates [23]. The fourth study supporting a non-salt-restriction policy was conducted by Morando *et al.* in 2015. They assessed patient adherence to moderately sodium-restricted diets (≤ 90 mmol/day) using a questionnaire and found that most patients did not adhere to such diets. Moreover, approximately half of the patients lacked definitive knowledge of the sodium content in different foods, believing they were on low-sodium diets when they were, in fact, consuming double the recommended amount [24].

In conclusion, managing dietary sodium intake in patients with liver cirrhosis is a complex issue with potential consequences for both malnutrition and ascites control [17]. It should be approached with caution, as it presents a double-edged sword in this patient population. Nonetheless, further research is needed to elucidate this contentious topic in the management of liver cirrhosis [25].

Reconsidering fluid restriction in cirrhosis patients with ascites

Fluid intake represents a challenge in patients with chronic liver diseases, particularly cirrhosis [26]. This dilemma stems from the liver's crucial role in managing fluid balance within the body. When the liver is impaired, there is an increased risk of fluid retention [26].

Patients often choose to limit their water intake when dealing with ascites, a practice commonly adopted in the absence of clear medical guidance due to concerns about further fluid accumulation. However, this approach can have unintended consequences. Restricting water intake can potentially lead to increased hypovolaemia, which triggers an exaggerated release of the antidiuretic hormone, a hormone that is already elevated in these patients. This, in turn, can further compromise kidney function and worsen hyponatraemia [27].

Most experts concur that there is no justification for water restriction in patients with uncomplicated ascites. However, the practice of restricting water intake

in patients with ascites and hyponatraemia is prevalent in many medical centres. Consensus guidelines restrict water intake control in ascites patients to those who are severely hyponatraemic despite diuretic therapy and exhibit normal kidney function [18]. Fluid restriction to 1–1.5 l/day should be reserved for those who are clinically hypervolaemic and have severe hyponatraemia (serum sodium less than 120 to 125 mEq/l) [18].

The challenge arises in the intermediate cohort with serum sodium levels ranging from 125 to 130 mEq/l, where making a well-informed decision becomes more complex [28]. In this context, the most sensible approach might involve water restriction with concurrent cessation of diuretics, rather than tolerating the adverse effects of impaired kidney function.

The issue of water restriction in patients with liver cirrhosis remains an unaddressed concern with a scarcity of studies investigating this matter. Therefore, it is imperative for researchers and academics to dedicate more efforts to resolve this critical dilemma.

Contemplation of micronutrients in patients with liver cirrhosis

Micronutrients play a vital role in supporting overall health, immune function, and the management of complications linked to liver cirrhosis [29]. Deficiencies in vitamins and trace elements are prevalent in cirrhosis, regardless of its underlying cause. Individuals with liver cirrhosis often experience reduced vitamin reserves compared to the general population, primarily stemming from hepatic dysfunction, inadequate dietary intake, diminished absorption, and heightened catabolism. Furthermore, micronutrient deficiencies are exacerbated by factors such as malabsorption, maldigestion, and the usage of diuretics [30].

Specific considerations in patients with liver cirrhosis are paid to vitamin A, which is essential for vision, immune function, and skin health [31]; vitamin K, necessary for blood clotting and bone metabolism, with liver dysfunction potentially leading to reduced synthesis [32]; vitamin E, an antioxidant whose absorption may be reduced in cirrhosis, contributing to oxidative stress; the B-vitamin complex, crucial for energy metabolism, nerve function, and red blood cell production, with deficiencies linked to fatigue and anaemia [32]; zinc, important for immune function and wound healing, with cirrhosis potentially reducing absorption; selenium, an antioxidant whose deficiency may contribute to oxidative stress and infection risk and responsible for the dysgeusia contributing to malnutrition in liver cirrhosis patients [33] (in cirrhotic patients with Child-Pugh score B or C and a model of end-stage liver disease (MELD) score ≥ 15, zinc deficiency is widespread, and it significantly correlates with disease severity, infection risk, and poorer transplant-free survival, underscoring the importance of screening for zinc deficiency in this specific patient subgroup) [34]; copper, essential for iron metabolism and brain function, with disruption in cirrhosis potentially leading to accumulation and neurological symptoms [35]; iron, vital for oxygen transport, with cirrhosis impacting its metabolism, leading to overload or deficiency [36]; and magnesium, crucial for muscle and nerve function, bone health, and energy production, with cirrhosis potentially causing deficiencies contributing to muscle cramps and cardiovascular complications [29]. In a recent study monitoring patients with decompensated cirrhosis, a high prevalence of micronutrient deficiencies, notably vitamin D (94.5%), vitamin A (93.5%), vitamin B_6 (60.8%), and zinc (85.6%) was seen, with significant variations in levels based on Child-Pugh class and MELD score [29]. Severe hepatic insufficiency is associated with lower zinc, vitamin E, and vitamin A levels, and elevated vitamin B_{12} and ferritin levels, underscoring the need for tailored nutritional interventions in this population to improve prognosis and mortality outcomes [29]. Addressing these deficient micronutrients is integral in optimising the nutritional support and overall well-being of individuals with liver cirrhosis.

Appraisal of the role of vitamin D in patients with chronic liver disease

In individuals experiencing chronic liver conditions, the occurrence of vitamin D deficiencies is notably elevated and nearly ubiquitous. Approximately 93% of those with chronic liver disease exhibit insufficient levels of vitamin D, with nearly one-third of this population displaying severe deficiency [37]. It has been linked to the onset and progression of NAFLD and chronic viral hepatitis progression and non-response to treatment [37]. Unlike other vitamins, vitamin D functions as a pre-hormone, undergoing conversion to its active hormone form, calcitriol, with the assistance of the liver and kidneys [38]. Essentially, the diminished levels of vitamin D are linked to malnutrition and limited sunlight exposure [38]. Additionally, liver conditions are characterised by reduced intestinal absorption of vitamin D and lower levels of binding proteins (DBP and albumin) crucial for transporting the hormone to the liver and kidneys for activation. Furthermore, impaired hepatic hydroxylation of vitamin D results in decreased production of the active hormone, while heightened catabolism of the vitamin exacerbates the deficiency [38]. Various clinical applications of 25(OH)D levels in chronic liver disease have been proposed. These include its potential use

as a non-invasive marker for liver fibrosis in chronic hepatitis C, as well as a prognostic factor for mortality and infections in individuals with liver cirrhosis [39]. Additionally, it may serve as a marker indicating an unfavourable outcome and advanced disease stage in hepatocellular carcinoma patients [40]. Malham *et al.* underscored the significance of monitoring vitamin D levels, particularly in cirrhotic populations, and especially those with alcoholic liver cirrhosis [41]. They also discussed the potential benefits of treatment for liver insufficiency-associated bone disease and the extra-skeletal advantages such as improved muscle function, reduced cancer risk, and enhanced immune function. The authors suggested the possible benefits of higher-than-standard doses of vitamin D supplementation for repletion [41]. Garcia-Alvarez *et al.* similarly recommended vitamin D screening for patients with hepatitis C virus (HCV) [42]. Conclusively, vitamin D as an antifibrotic and anti-inflammatory agent played a substantial role in patients with chronic liver disease, with improved quality of life and outcomes on supplementation. Accordingly, screening and supplementation of vitamin D in patients with diseased liver, whatever the aetiology, is mandatory.

Reconsidering the role of mobility in cirrhotic patients

Prescribing reduced physical activity for individuals with chronic liver disease can have a significant impact on their overall well-being and quality of life. Physical activity plays a crucial role in preserving muscle mass and mitigating the detrimental effects of sarcopaenia [43].

Patients with chronic liver disease often struggle with symptoms such as fatigue and weakness, making it challenging for them to engage in regular exercise or perform daily tasks [44]. This can lead to progressive muscle atrophy, declining physical function, and eventually frailty and sarcopaenia [45]. Unfortunately, misguided medical advice promoting patient inactivity may contribute to the worsening of their condition.

Moreover, reduced mobility can also predispose patients to the development of other health issues, such as obesity, diabetes, and cardiovascular diseases [46]. Therefore, it is imperative that patients with compensated advanced chronic liver disease (cACLD) in its early stages are encouraged to maintain their regular physical activity without unnecessary restrictions. For those with advanced liver disease, it is advisable for them to collaborate with their healthcare providers to design a safe and tailored exercise program suited to their specific needs. This program may incorporate low-impact activities such as walking or swimming, along with resistance training to preserve muscle mass.

Valuation of regular screening of chronic liver disease complications

Screening for oesophageal varices (OV)

In patients with cACLD, screening for oesophageal varices (EV) is a critical component of their care. According to the Baveno VII criteria, non-invasive methods such as transient elastography (TE) are recommended when liver stiffness is ≥ 20 kPa or when the platelet count is ≤ 150 × 10^9/l to identify clinically significant portal hypertension (CSPH) [47]. In cases where these tests yield inconclusive results, upper endoscopy should be performed to confirm the presence of varices. This screening is vital because EV can lead to life-threatening bleeding, and early detection enables the adjustment of treatment strategies to prevent further complications. Common interventions for primary, secondary, or tertiary prevention of EV include band ligation or the use of non-selective β-blockers (NSBBs) such as classic or carvedilol [48].

Screening for fibrosis progression

Monitoring the progression of fibrosis in patients with chronic liver disease is crucial for overall health management. Cirrhosis is a severe complication that can result from untreated liver disease, and early detection of fibrosis is key to preventing its advancement. Various screening methods are available, including blood tests (both direct and indirect markers of liver fibrosis), imaging studies, and liver biopsies [49]. The choice of screening method depends on individual patient needs and medical history. Formulas or scores, especially those combining both direct and indirect fibrosis markers, have shown excellent performance in determining fibrosis stage. Notably, the Fib4 formula is widely used and has high sensitivity [50]. Regular monitoring is essential for patients with chronic liver disease, to ensure early detection of any changes in their condition, enabling the initiation of appropriate treatment.

Screening for decompensation

Vigilant screening for decompensation in patients with compensated liver cirrhosis is essential for their ongoing care. Decompensation refers to the deterioration of liver function and can lead to serious complications such as ascites, hepatic encephalopathy, and variceal bleeding [47]. Regular monitoring of liver function tests, imaging studies, and clinical symptoms is necessary to detect early signs of decompensation and facilitate timely intervention. Scores like Child-Turcotte-Pugh (CTP), model of end stage liver disease (MELD), MELD-Na, the recently developed platelet-albumin-bilirubin (PALBI) score, and the albumin-bilirubin (ALBI) score

all have gained popularity as simple and reliable scores predicting cirrhosis outcomes [50]. Additionally, addressing underlying factors contributing to decompensation, such as alcohol use, medication toxicity, or infections, is crucial. According to the Baveno VII criteria, the presence of clinically significant portal hypertension (CSPH) distinguishes between cACLD and decompensated advanced chronic liver disease (dACLD), marking the point at which deterioration begins [47]. Therefore, patients with a hepatic venous pressure gradient (HVPG) ≥ 10 mm Hg should anticipate the likelihood of a first decompensation event, particularly bleeding oesophageal varices, and may benefit from preventive measures such as NSBBs, or classic or more potent carvedilol. The reliance on non-invasive indicators of CSPH, such as liver stiffness measured by TE, where values > 15 kPa are highly suggestive of cACLD, can be an informative screening tool. For patients with intermediate liver stiffness values (between 10 and 15 kPa), it is important to consider CSPH as a possibility. Notably, patients with an LSM by TE < 10 kPa have a minimal 3-year risk (≤ 1%) of decompensation and liver-related death [47]. Emphasising the "rule of 5" for LSM by TE (10-15-20-25 kPa) underscores the ongoing risk of decompensation. LSM values ≥ 25 kPa are highly diagnostic of CSPH, while values between 20 and 25 kPa with a platelet count < 150 × 10^9/l or LSM values between 15 and 20 kPa with a platelet count < 110 × 10^9/l carry a high probability of CSPH (60%) [47].

In summary, sequential screening for decompensation is a vital aspect of managing patients with compensated liver cirrhosis to predict and prevent further deterioration.

Screening for minimal hepatic encephalopathy (MHE)

The screening for MHE holds paramount significance in the comprehensive management of patients with liver cirrhosis. MHE is characterised by cognitive impairment, which can profoundly impact a patient's quality of life and daily functioning [50]. Early detection through screening tests is of critical importance because it enables timely initiation of treatment and prevents the progression of the disease to overt hepatic encephalopathy. It is worth noting that patients with MHE have been found to have a higher incidence of vehicle accidents [51, 52].

Multiple non-invasive screening tests are available for MHE, including the psychometric hepatic encephalopathy score (PHES), inhibitory control test (ICT), critical flicker frequency (CFF), and the Stroop test. These tests can be easily administered in an outpatient setting [53]. It is recommended that all patients with liver cirrhosis undergo regular screening for MHE, especially those with a history of hepatic encephalopathy, individuals who drive as part of their daily activities, and those who have undergone a liver transplant. Screening should also be considered for patients with advanced liver disease or those at high risk of developing MHE [54].

In conclusion, screening for minimal hepatic encephalopathy is a crucial element of the management of patients with liver cirrhosis. Early detection through screening tests is vital for timely treatment initiation and the prevention of disease progression.

Screening for hepatocellular carcinoma (HCC)

Screening for HCC is a pivotal aspect of the comprehensive care for patients dealing with liver cirrhosis. HCC is a common form of liver cancer that frequently arises in individuals with cirrhotic liver, a condition characterised by progressive liver scarring and damage. The adoption of routine screening protocols, which may include ultrasound assessments alone or in conjunction with α-fetoprotein testing, plays a crucial role in the early detection of HCC, thereby enhancing the prospects of successful treatment. However, the frequency and timing of these screenings should be tailored to the specific risk factors and medical history of each patient [55]. Healthcare providers must, therefore, work closely with their patients to formulate a personalised screening strategy that accommodates their unique needs and circumstances.

Screening for sarcopaenia

Sarcopaenia, initially defined by the European Working Group on Sarcopaenia in Older People (EWGSOP) as a condition characterised by decreased muscle mass and power, has been redefined to prioritise low muscle strength as its foundational element [12]. In the context of liver cirrhosis, screening for sarcopaenia is a crucial component of patient care due to its high prevalence as a common complication [56]. Sarcopaenia in this population can lead to adverse outcomes, including increased morbidity and mortality [56]. Consequently, early identification and intervention are of paramount importance in improving patient outcomes [56]. Several screening methods exist for identifying sarcopaenia in these individuals, including bioelectrical impedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA). However, it is worth noting that these tools are not readily accessible in routine medical practice [57]. Moreover, although computed tomography (CT) scanning is a valid choice, it is burdened by radiation risks and substantial costs, which diminish its feasibility for broad application [57]. A promising role of ultrasonog-

raphy in defining sarcopaenia has been advocated with satisfactory performance as a cheap, accurate, available, and mobile diagnostic and screening tool [58]. However, determining the optimal screening method for sarcopaenia in liver cirrhosis patients remains a subject of ongoing debate and requires further research.

Screening for diabetes mellitus (DM)

Metabolic dysfunction and insulin resistance frequently manifest in patients with liver cirrhosis, with approximately 30% of individuals suffering from liver cirrhosis also experiencing DM [59]. The relationship between liver cirrhosis and DM presents in various forms, with hepatogenous DM being the most common connection [60]. Patients with advanced liver disease, including cirrhosis, face a heightened risk of developing DM and subsequent hypoglycaemia due to impaired liver function, which plays a pivotal role in regulating glucose levels in the body [61, 62]. The presence of DM in liver cirrhosis patients adds complexity to disease progression, contributing to increased morbidity and mortality [63]. Remarkably, patients with both cirrhosis and DM are at a higher risk of developing HCC [64]. Despite ongoing discussions, there remains no consensus on the optimal therapeutic approach, with medication choices contingent on factors such as the underlying cause and severity of liver cirrhosis, the degree of insulin resistance, the risk of hypoglycaemia, and the patient's nutritional status [65].

Managing DM in malnourished liver cirrhosis patients presents a complex and challenging task. In addition to pharmacological treatments, dietary interventions play a vital role in the care of individuals with liver cirrhosis and DM. A well-balanced diet that provides sufficient calories, protein, carbohydrates, fats, vitamins, and minerals is essential for preventing malnutrition and sustaining liver function. However, dietary recommendations may differ depending on the aetiology and stage of liver cirrhosis. For instance, patients with metabolic dysfunction-associated steatotic liver disease (MASLD) or metabolic dysfunction-associated steatohepatitis (MASH) may benefit from a low-carbohydrate, high-protein diet that can reduce insulin resistance and hepatic steatosis [66]. Conversely, individuals with decompensated liver cirrhosis may require a low-protein, high-carbohydrate diet to mitigate ammonia production and hepatic encephalopathy [67].

In such cases, reliance on oral antidiabetic medications can be fruitful in achieving blood sugar control [68]. However, the clinical implications of these medications and their impact on the progression of liver disease remain subjects of debate. The liver plays a pivotal role in drug metabolism and elimination from the body [69]. In advanced liver dysfunction, drug metabolism is impaired, leading to the accumulation of medications in the body. Hypoalbuminaemia can exacerbate this issue by increasing the free plasma concentration of drugs [70]. Moreover, these patients often exhibit insulin resistance, which can result in hypoglycaemia due to impaired insulin-mediated glucose uptake [71]. Therefore, dose adjustments, close monitoring of drug levels, and regular assessment of liver function are imperative for effective management.

Notably, individuals with chronic liver disease (CLD) are more susceptible to acute kidney injury (AKI) due to factors such as drug or metabolite accumulation [72]. This heightened risk in CLD patients can be attributed to impaired drug metabolism and excretion, altered renal blood flow, and systemic inflammation associated with liver dysfunction. It underscores the increased vulnerability of CLD patients to AKI due to impaired renal function and highlights the role of drug accumulation in this population [73].

It is important to emphasise that insulin therapy remains the safest choice for individuals with advanced CLD. Some studies recommend insulin for diabetes management in patients with liver cirrhosis, particularly in cases of acute decompensation or hepatic encephalopathy [74]. However, other research suggests that insulin use may be associated with higher risks of mortality, liver-related complications, cardiovascular events, and hypoglycaemia compared to non-users [75]. Therefore, insulin therapy should be employed cautiously and with close monitoring in individuals with liver cirrhosis and DM [76].

Additionally, various other antidiabetic agents, such as metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter-2 inhibitors, have been used in individuals with liver cirrhosis and DM [62]. However, their safety and efficacy in this population are not well-established, and some may have adverse effects on liver function or increase the risk of lactic acidosis or hepatotoxicity [63]. Therefore, these agents should also be used cautiously, with dosage adjustments made for individuals with liver cirrhosis and DM.

In summary, the management of DM in malnourished liver cirrhosis patients requires a comprehensive and individualised approach that considers the aetiology and severity of liver cirrhosis, the degree of insulin resistance, the risk of hypoglycaemia, and the patient's nutritional status. Insulin therapy may be indicated in some cases but should be administered with caution and close monitoring. Other antidiabetic agents may also be used but should be adjusted based on liver

function and potential adverse effects. Dietary interventions are crucial for preventing malnutrition and maintaining liver function, but they should be tailored according to the stage and complications of liver cirrhosis.

Addressing obesity and BMI control in liver cirrhosis patients

The intricate and bidirectional relationship between obesity and chronic liver disease significantly heightens the risk of liver cirrhosis development [77]. Current understanding suggests that numerous individuals diagnosed with cryptogenic cirrhosis are likely in the advanced phases of nonalcoholic fatty liver disease. The projection is that liver diseases associated with obesity will emerge as the predominant cause of liver failure and transplantation [78]. It is essential for individuals who are overweight or obese to actively manage their body mass index (BMI) to reduce the likelihood of progressing to liver cirrhosis, HCC, and/or decompensation [79]. Moreover, obesity serves as a known risk factor for gallstones, leading to recurrent obstructions and cholangitis [80]. This connection between obesity, liver cirrhosis, and gastroesophageal reflux oesophagitis (GERD) often results in significant suffering for affected individuals [80]. Acute pancreatitis and pancreato-biliary malignancies have also shown strong associations with obesity [81]. Furthermore, the suggested link between obesity and portal and hepatic vein thrombosis, as part of generalised thromboembolism in liver cirrhosis, remains the subject of ongoing debate [82].

Of particular concern is the condition known as sarcopaenic obesity, representing the most challenging clinical scenario for cirrhotic patients, carrying a high risk of physical impairment, disability, and a multitude of comorbidities surpassing the risk posed by either condition alone [83]. Numerous studies underscore the pivotal role of weight control in reversing chronic liver disease [84].

Despite not being a contraindication for liver transplantation, obesity significantly complicates pre-, intra-, and post-operative management [85]. Post-transplantation, reduced muscle activity, immunosuppressive agents that hinder skeletal muscle growth and protein accretion, along with a return to the normal catabolic state, often result in a sarcopaenic-obese post-transplant candidate [86]. The multifactorial nature of post-transplantation metabolic syndrome further compounds the complexity of the condition, leading to an increased risk of complications [87].

Dietary adjustments and exercise regimens remain the primary means of obesity control in patients with liver cirrhosis, whether their condition is compensated or decompensated [72]. Importantly, for cirrhotic patients with morbid obesity, bariatric surgery may be considered as a last resort. In some cases, these surgeries can be performed concurrently with liver transplantation, offering patients not only a new liver but also a healthier body [87]. However, it is worth noting that bariatric surgery has been associated with triggering acute liver failure and high morbidity rates in some reports [88, 89].

Unveiling the risks of improper and continuous proton pump inhibitor (PPI) usage

Proton pump inhibitors (PPIs) are frequently prescribed to manage conditions like GERD, other acid-related disorders, and gastrointestinal bleeding (GIB). However, their continuous and inappropriate use in patients with chronic liver disease can have detrimental effects [90]. Firstly, they increase the risk of infections by reducing stomach acidity, leading to bacterial overgrowth and gut infections, which can exacerbate hepatic encephalopathy and spontaneous bacterial peritonitis, ultimately increasing mortality [91]. This is especially concerning in patients with chronic liver disease who already have compromised immune systems [91].

Secondly, PPIs have been shown to elevate certain liver enzymes, potentially causing liver damage and worsening liver function in patients with chronic liver disease [92]. Thirdly, long-term PPI use has been linked to an increased risk of fractures, particularly in older adults and those with osteoporosis, which is a concern for patients with chronic liver disease who may already be at higher risk of fractures [93]. Fourthly, PPIs can interfere with the absorption of essential nutrients like calcium, magnesium, and vitamin B_{12}, potentially leading to nutritional deficiencies that further worsen the health of chronic liver disease patients [94]. Steatosis and weight gain have also been reported as metabolic dysfunctions related to PPI misuse [95]. There is also an association between prolonged PPI use and an increased risk of HCC in patients with liver cirrhosis [96].

Moreover, PPIs can interact with other medications commonly used in liver disease patients, emphasising the need for a careful review of the medication list and potential interactions with a specialist [97]. Lastly, the inappropriate and continuous use of PPIs in chronic liver disease patients can lead to increased healthcare costs due to frequent hospitalisations for infections, deteriorating liver function, and encephalopathy [98–100].

Patients with chronic liver disease, whether compensated or decompensated, typically require lower PPI doses and should use these medications for the shortest duration necessary to manage their underlying condition. Recent reports have highlighted the potential benefits of PPIs in managing gastrointestinal bleeding

and reducing all-cause mortality [91]. Therefore, PPIs should not be avoided in cirrhosis solely out of concern for liver-related adverse outcomes. Instead, prescription should be limited to appropriate indications at the lowest effective dose. Continuous and unjustified long-term use of PPIs should be discouraged or discontinued when not medically necessary.

The choice of PPI and its maximum dose for patients with chronic liver disease should be individualised, considering the patient's specific liver function and other relevant factors. Commonly used PPIs include omeprazole (typically starting with a lower dose of 20 mg/day), esomeprazole (up to 40 mg/day), lansoprazole (starting dose of 15–30 mg/day), pantoprazole (generally up to 40 mg/day), rabeprazole (usually up to 20 mg/day), and dexlansoprazole (typically up to 60 mg/day, with adjustments based on individual needs) [101, 102].

In conclusion, patients with chronic liver disease, whether they have compensated or decompensated cirrhosis, require specialised care in highly specialised centres, with a multidisciplinary team that includes hepatologists, endoscopists, radiologists, dietitians, diabetologists, physiotherapists, oncologists, and surgeons. Malnutrition is a critical factor that impacts liver disease progression and complications, and dietary recommendations can lead to significant improvements. Implementing well-designed, sustainable screening programs at regular intervals is essential for early detection and proper management of liver disease risks and complications.

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Conflict of interest

The authors declare no conflict of interest.

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