ASSESSMENT OF NUTRITIONAL STATUS AND MANAGEMENT OF SARCOPENIA IN CHRONIC LIVER DISEASE

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Outline

- Introduction
- Pathophysiology
- Nutritional assessment
- Management
- Take home message

Introduction

- In **1988, Irwin Rosenberg** proposed that sarcopenia **is age related decrease of skeletal muscle mass (SMI) and function**. The term sarcopenia is still largely unknown among clinicians and researchers.

- It is Greek phrase for '**poverty of flesh'**

- It is usually accompanied by physical inactivity, decreased mobility, slow gait, and poor physical endurance which are also common features of the frailty syndrome.

- The prevalence of sarcopenia ranged from **13 to 24% in persons aged 65 to 70** years and was **over 50%** for those older than **80 years**

- The prevalence of **sarcopenia** within patients with **chronic liver disease (CLD)** is estimated at **~25%–70%,** with higher rates identified among males

- The presence of sarcopenia imposes significant **clinical complica**tions and has been associated with **increased mortality** , **reduced quality of life (QoL),** increased **length of hospital stays** , and development of complications such as **infections, both pre- and post liver transplant (LT)**

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Definitions and terminology

Malnutrition	A nutrition-related disorder resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass, leading to diminished physical and mental function and impaired clinical outcome from disease. In the present CPGs, we have used "malnutrition" as a synonym of "undernutrition"
Undernutrition	Synonym of malnutrition (see above)
Muscle wasting	The active, progressive loss of muscle mass due to an underlying disease, ultimately leading to muscle atrophy. Most inflammatory diseases, malnutrition and increased catabolism induce muscle wasting
Sarcopenia	A generalised reduction in muscle mass and function due to aging (primary sarcopenia), acute or chronic illness (secondary sarcopenia), including chronic liver disease
Frailty	Loss of functional, cognitive, and physiologic reserve leading to a vulnerable state. Frailty may be considered a form of nutrition-related disorder

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DEFINING MALNUTRITION IN CIRRHOSIS

- Malnutrition is frequently a burden in patients with liver cirrhosis, occurring in **20–50% of patients**

- Malnutrition has been reported in **20%** of patients with **compensated cirrhosis** and in more than **50%** of patients with **decompensated liver disease**

- Malnutrition and muscle mass loss (sarcopenia), are associated with a higher rate of complications such as susceptibility to **infections**, hepatic encephalopathy (**HE)** and **ascites,** as well as being independent predictors of **lower survival** in **cirrhosis** and in patients undergoing liver transplantation

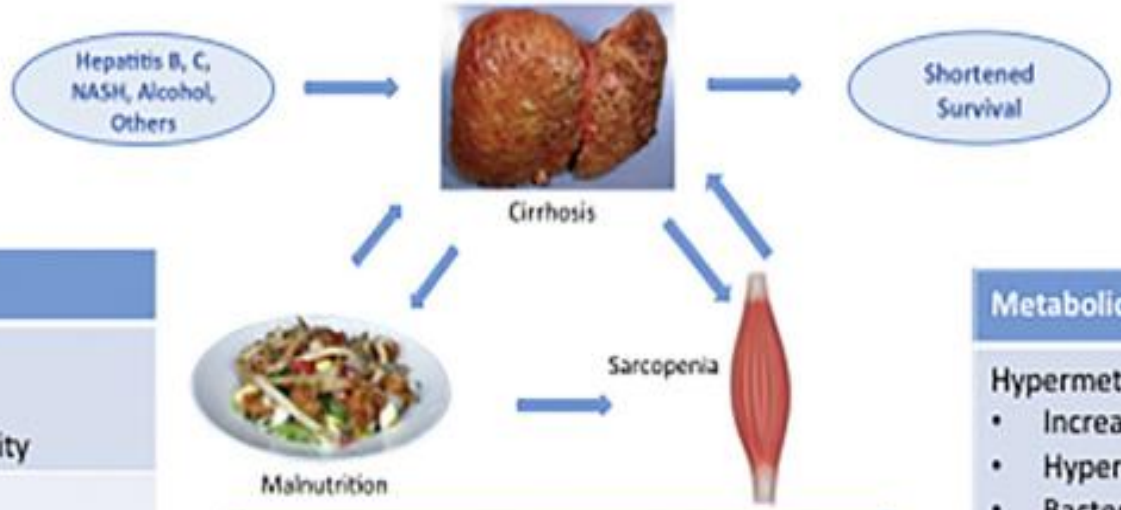
PATHOGENESIS AND PATHOPHYSIOLOGY

- There are **several factors** for a patient of cirrhosis to be **malnourished** which are concluded in the three following spectrum that affects the nutritional status:

1- Inadequate dietary intake

2- Malabsorption

3- Metabolic disturbance



Inadequate dietary intake

Nausea and early satiety
- Ascites
- Impaired gastric and gut motility

Loss of appetite
- Upregulation of Leptin and TNF-α

Altered Taste
- Zinc deficiency

Dietary restriction
- Salt restriction
- Fasting for clinical investigation
- Protein restriction for hepatic encephalopathy

Alcohol dependence
- Irregular and poor eating

Malabsorption

Portosystemic shunting

Chronic pancreatitis
- Associated due to alcohol abuse

Bile acid deficiency
- Decreased production
- Portosystemic shunting

Small intestinal bacterial overgrowth

GI Bleeding
- Hypermotility
- Loss of protein

Metabolic disturbances

Hypermetabolic state
- Increased sympathetic system activity
- Hyperdynamic circulation
- Bacterial translocation from gut

Physical inactivity
Obesity and other endocrine factors

Associated Sepsis and cytokine storm

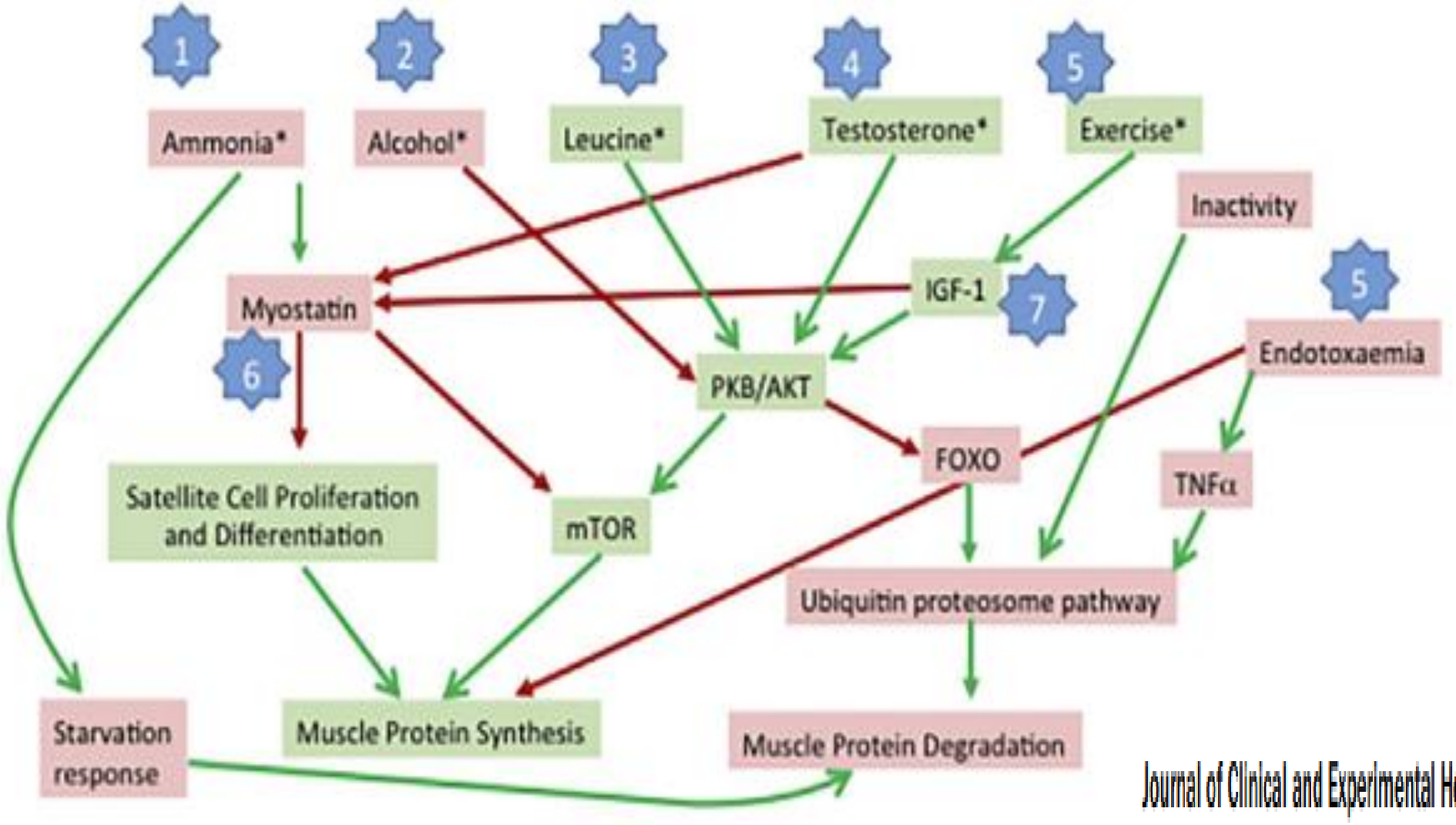
Increased gluconeogenesis
- Lack of glycogen storage
- Breakdown of fat and muscles

- Liver cirrhosis causes an **accelerated state of starvation** with increased **gluconeogenesis**, **fat oxidation**, **ketogenesis** and **catabolic state**

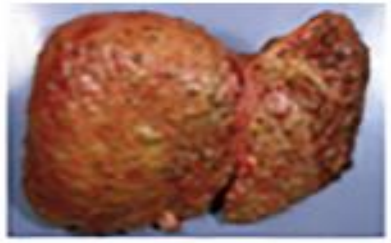
- Due to multifactorial processes such as impairment in **protein turnover**, **dysbiosis**, malnutrition, **hyperammonaemia** and **chronic inflammation**

- Also associated with alterations in the endocrine system such **hypotestosteronaemia** and impaired **insulin/IGF-1** pathway

Skeletal muscle mass is maintained by a balanced relationship between protein synthesis ,proteolysis and satellite cells in muscles which are responsible for skeletal muscles regeneration



Starvation and Liver



State of Accelerated Starvation

Reduced Glycogen stores
Increased Gluconeogenesis

Increased fatty acid oxidation

Gluconeogenesis possible from AA and not FA

Only source of AA is proteolysis of muscle: Generates AAA and BCAA

Skeletal muscle can utilise only BCAA due to localisation of branched chain keto-dehydrogenase

AAA utilised only in liver (poor function, shunting): Low BCAA and High AAA concentration in plasma

Nutritional assessment in cirrhosis

- **Two simple criteria** stratify patients at **high risk of malnutrition**:

- **Being underweight**, defined as a body mass index (BMI) (kg. Body weight [BW]/[height in meters]2) < 18.5 kg/m2

- Having **advanced decompensated cirrhosis** (Child-Pugh C patients).

- The above criteria should have **detailed nutritional assessment**. This is to identify patients **at risks**, confirm presence and **severity of malnutrition**

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Nutritional screening

- There are two liver disease specific nutritional screening tools:

A. The Royal Free Hospital-nutritional prioritizing tool (RFH-NPT) score

- (RFH-NPT) score was reported to correlate with clinical deterioration, severity of disease (Child-Pugh score, model for end-stage liver disease [MELD] score), and clinical complications such as ascites, hepatorenal syndrome, and episodes of HE

B. The liver disease under-nutrition screening tool

- Is based on six patient-directed questions regarding: nutrient intake, weight loss, subcutaneous fat loss, muscle mass loss, fluid accumulation and decline in functional status

- Patients who at risk for malnutrition during screening should undergo a detailed nutritional assessment (include muscle mass , global assessment tool and detailed dietary intake assessment

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Nutritional assessment

- **A. Dietary interviews**

A detailed assessment of dietary intake : food, fluids, supplements, number of meals and their timing throughout the day (e.g. interval between meals, breakfast and late-night meals as recommended), as well as calories and quality and quantity of protein intake

It Is time consuming, requires skilled personnel and relies on patient recall

- **B. Global assessment tools in cirrhosis include:**

subjective global assessment (SGA) and the Royal Free Hospital-global assessment (RFH-GA)

They are subjective, inaccurate and underestimates the prevalence of sarcopenia in cirrhosis.

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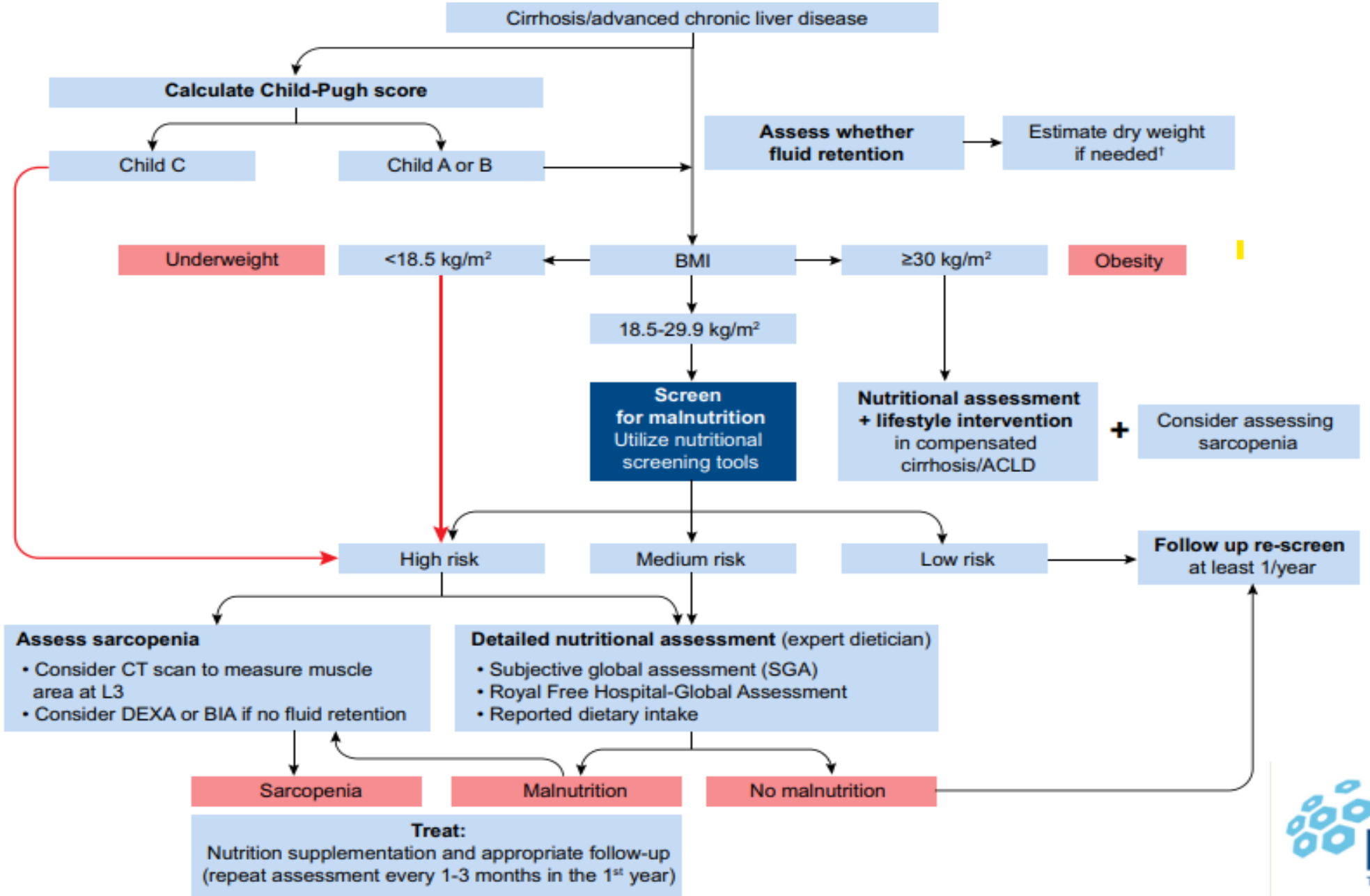

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Assessment of sarcopenia in CLD

- Sarcopenia is a major component of malnutrition. Direct quantification of skeletal muscle mass requires cross-sectional imaging. **Computed tomographic (CT)** image analysis at the **L3 vertebra**

- Analyses **cross-sectional area** of abdominal skeletal muscles at **L3 vertebrae**, normalised to **height** to calculate the skeletal muscle index **(cm2/m2)**

- **Psoas muscle** and possibly **para spinal and abdominal wall muscles** are considered core skeletal muscles that are **relatively independent of activity and water retention**, but are consistently altered by the **metabolic and molecular perturbations** of cirrhosis.

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Skeletal Muscle Index

- Standardized cut-off values of SMI are **< 50 cm2/m2 in males** and **< 39 cm2/m2 in women** to define sarcopenia

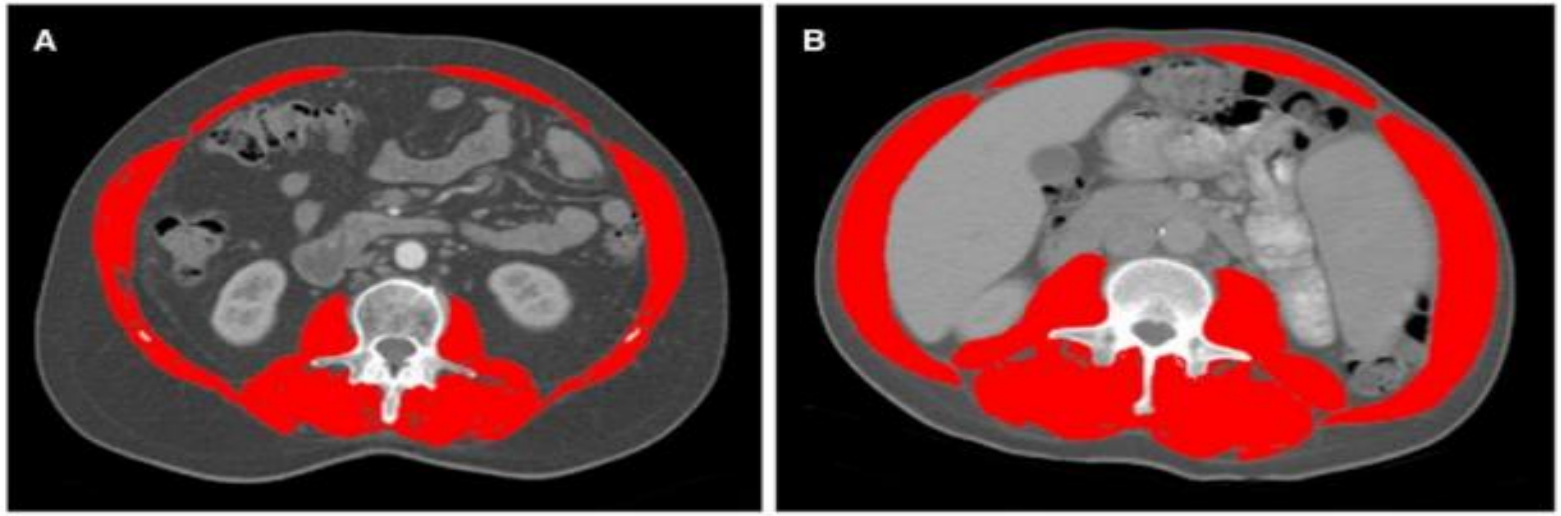

FIG. 1. Total muscle area quantification at the level of third lumbar vertebra using abdominal CT images from two male patients with cirrhosis. (A) and (B), respectively, present a patient who had low SMI (46 cm^2/m^2) and high SMI (60 cm^2/m^2) as indicated by the red shading.

Assessment of sarcopenia in CLD

- The routine use of CT imaging for repeated assessments, is obviously limited in clinical practice due to **cost** and exposure to **radiation**

- Other modalities include **BIA , DEXA scan, Anthropometry** and **muscle ultrasound**.

- **Bioimpedance analysis (BIA)** is affected by Fluid retention affecting the reliability of lean body mass estimates.

- **Anthropometric measurements** including **BMI** and **MAMC** are poor indicators of nutritional status due to **inability to differentiate fat** from **muscle mass and fluid retention**

- **Dual energy x-ray absorptiometry (DEXA)** is unable to differentiate **water from muscle** , as result edema falsely elevates muscle mass measurements

- **Laboratory tests** for evaluating nutritional status in the general population such as **serum albumin** are generally affected **hepatic dysfunction**

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Table 1 Summary of Investigations Done for Assessment of Sarcopenia.

Variable	Muscle mass	Muscle strength	Performance
Research	• Computed tomography (CT) • Magnetic resonance imaging (MRI) • Dual energy X-ray absorptiometry (DXA) • Bioimpedance analysis (BIA) • Total or partial body potassium per fat-free soft tissue	• Handgrip strength • Knee flexion/extension • Peak expiratory flow	• Short Physical Performance Battery (SPPB) • Usual gait speed • Timed get-up-and-go test • Stair climb power test
Clinical practice	• BIA • DXA • Anthropometry • CT L3 SMI	• Handgrip strength • Frailty scores	• SPPB • Usual gait speed • Get-up-and-go test

Micronutrient deficiency

- In patients with decompensated cirrhosis, it is advisable to conduct a comprehensive evaluation of micronutrient status at **least on an annual basis**

- In instances where such assessments are not feasible, the administration of an **empiric regimen** of oral multivitamin supplementation is recommended

- This supplementation should encompass **fat-soluble vitamins** (including vitamins A, D, E, and K), **water-soluble vitamins** (notably folate and vitamin B12), as well as essential **trace elements** such as magnesium, selenium, and zinc

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Nutritional management principles in CLD

- Management should be conducted by a **multidisciplinary team** that includes a **qualified dietitian**
- Approach with specific focus on **lifestyle, nutrition, exercise** and **pharmacotherapy**
- The primary objective is to ensure **sufficient caloric** and **protein consumption**
- This strategy is particularly relevant for **sarcopenic obese patients with cirrhosis**, aiming to promote weight reduction while **preserving muscle protein reserves**

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Nutrition

- Evidence suggests that **high-energy**, **high protein diet** improves **nitrogen** balance

- **Optimal daily energy intake** should not be lower than the recommended **35 kcal/kg.** actual BW/d (**in nonobese individuals**)

- **Optimal daily protein** intake should not be lower than the recommended **1.2–1.5 g/kg**. actual BW/d

- The daily intake should be divided into **frequent small meals** and/or **snacks 5-6 times** a day

Nutrition

- In patients with malnutrition and cirrhosis who are **unable to achieve adequate** dietary intake with the **oral diet** (even with oral supplements), a **period of enteral nutrition** is recommended

- **Moderately hypocaloric** (-500–800 kcal/d) diet, including **adequate protein intake** (>1.5 g proteins/kg. ideal BW/d) can be adopted to achieve weight loss without **compromising protein stores** in **obese cirrhotic patient**

- Some studies support the use of **BCAAs supplements** in management of cirrhosis, especially when adequate nitrogen intake is not achieved (**long-term BCAA 0.25g/kg/D improves events free survival**)

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Nutrition

- Assess **vitamin D levels** in cirrhotic patients, as deficiency is highly prevalent and may adversely affect **clinical outcome**

- **Supplement vitamin D orally** in cirrhotic patients with vitamin D levels less than 20 ng/ml ,to reach serum vitamin D (25(OH)D) >30 ng/ml.

- In **cirrhotic patients with ascites** under sodium restriction (recommended intake of **sodium 80 mmol day = 2 g of sodium corresponding to 5 g of salt** added daily to the diet according to EASL guidelines)

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Nutritional treatment options for hepatic encephalopathy

- **Nutritional status** and the presence of **sarcopenia** should be evaluated in patients with **HE**

- **Oral dietary intake** is preferred in patients who **can tolerate it**. In patients with **grade III-IV encephalopathy**, who are unable to eat, provide nutrition by **nasogastric tube**

- **BCAA supplementation** should be considered to improve **neuropsychiatric performance** and to reach the recommended **nitrogen intake**

- Encourage the consumption of **vegetables** and **dairy protein**

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Nutritional treatment options in cirrhotic patients with bone diseases

- Evaluate **BMD in cirrhotic patients** and in patients with **cholestatic liver diseases**, those receiving long-term **corticosteroid treatment**, and before **liver transplant**

- Utilise lumbar and femoral densitometry **(DEXA)** to diagnose **osteoporosis and osteopenia**. Lateral X-rays of **dorsal and lumbar** spine for diagnosing **vertebral fractures**

- **Repeat DEXA** after two to three years in patients within **normal BMD**, and within **one year** when rapid bone loss is expected

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- Include **supplements of calcium** (1,000–1,500 mg/d) and **25(OH)D** (400–800 IU/d or 260 lg every two weeks) in patients with chronic **liver disease and a T-score below -1.5**

- Utilise **bisphosphonates** in cirrhotic patients with **osteoporosis** and in those waiting for **liver transplantation**

- Consider **testosterone supplementation** and **venesection** in males with **hemochromatosis** and **hypogonadism**

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Malnutrition in patients undergoing liver transplantation

- **Preoperatively**, if the treatment goal is **maintenance of nutritional status**, plan a total **energy intake** of **30 kcal/ kg.BW/d** and a **protein intake of 1.2 g/kg.BW/d**

- If **improvement of nutritional status is the goal**, plan a total **energy** intake of **35 kcal/kg.BW/d** and a **protein intake** of **1.5 g/kg.BW/d**

- **After liver transplantation** initiate **normal food and/or enteral tube** feeding preferably within **12–24 h postoperatively**, or as soon as possible, to **reduce infection rate**

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- When **oral or enteral nutrition** are not possible, **parenteral nutrition** should be used instead of no feeding in order to **reduce complication** rates, time on **mechanical ventilation** and **ICU stay**

- After the **acute postoperative phase**, provide an energy intake of **35 kcal/kg.BW/d** and a **protein intake** of **1.5 g/ kg.BW/d**

- Consider **parenteral nutrition** in patients with **unprotected airways** and **HE when cough and swallow reflexes are compromised**

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Exercise and physical activity

- In addition to **nutritional supplementation**, **increased physical activity** and **exercise** are also **anabolic stimuli** that can improve **muscle mass and function**

- **Resistance exercise** promotes an increase in **skeletal muscle mass**. However, **exercise** also increases muscle **ammonia generation** and **portal pressure**, both of which can have **adverse effects** in cirrhotic patients
- Aiming for a total of **150-200 minutes** per week, but There is no **specific evidence** supporting that **physical therapy** alone reverses sarcopenia

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Pharmacotherapy

- **Testosterone replacement** therapy is advised for **men with cirrhosis** and **sarcopenia** who exhibit **low testosterone** levels, as it can help increase **muscle mass**

- **Testosterone** use is relatively **contraindicated** in individuals with a history of hepatocellular carcinoma **(HCC), malignancies**, or **thrombosis**

- Emerging treatments under investigation include **ammonia-lowering** drugs and **myostatin inhibitors**, though these are **still in the research** phase and have not yet been tested in human clinical trials

- Additional **suggested treatments** involve managing portal hypertension through the use of a transjugular intrahepatic portosystemic shunt **(TIPS)** and performing **liver transplantation**

- There is no evidence for use of **TIPS** and **liver transplant primarily** for the management of **sarcopenia or frailty**

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Treatment summary

Table 3 A Typical Prescription to Improve Nutrition in Patients with Cirrhosis. Therapies Marked with * are not Recommended for Routine Use but may be Tried in Context of Controlled Trials.

1. Abstinence from alcohol (take psycho-social and psychiatric help if required)
2. Diet
1.2–1.5 g of protein per kg of body weight per day (a third from dairy, vegetable protein and animal protein each). Total 35–40 kcal/kg intake per day
Suggest late evening snack and early breakfast consisting of complex carbohydrates and protein
Supplement branched chain amino acids
Use tube feeding (overnight continuous drip) or parenteral nutrition in critically ill patients
Zinc, vitamin D and other micronutrient deficiency to be corrected
3. Exercise regime consisting of resistance and aerobic exercised, gently increased in a graded manner as per patient's capacity
4. Normalization of porta pressure, nonselective beta-blockers or TIPS as indicated
5. Ammonia lowering measures
Rifaxamine, laculose, aKG, BCAA
6. Hormonal therapy
Testosterone, oxandrolone, growth hormone*
7. Innovative therapies
IGF-1, myostatin inhibitors, follostatin, antioxidants, DRP1 inhibitors*
8. Liver transplantation*

Take home messages

- **Sarcopenia common in liver cirrhosis**
- **Muscle loss in cirrhosis results from multiple factors**
- **Assessment of sarcopenia should be a routine part of cirrhosis management**
- **Testosterone helps if low levels, with caution**
- **Nutrition and exercise key treatments**
- **New drugs under research (ammonia-lowering, myostatin inhibitors)**
- **Early, multidisciplinary care improves outcomes**

Thank you

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