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From liver to hormones: The endocrine consequences of cirrhosis

Quiroz-Aldave JE *et al.* The endocrine consequences of cirrhosis

Abstract

BACKGROUND

Hepatocrinology explores the intricate relationship between liver function and the endocrine system. Chronic liver diseases such as liver cirrhosis can cause endocrine disorders due to toxin accumulation and protein synthesis disruption. Despite its importance, assessing endocrine issues in cirrhotic patients is frequently neglected. This article provides a comprehensive review of the epidemiology, pathophysiology, diagnosis, and treatment of endocrine disturbances in liver cirrhosis.

AIM

To provide an update on the epidemiology, pathophysiology, diagnosis, and treatment of endocrine disturbances caused by cirrhosis.

METHODS

A narrative review was conducted using the PubMed/Medline, EMBASE, and Scielo databases, encompassing 172 articles.

RESULTS

Liver cirrhosis is associated with endocrine disturbances, including diabetes, hypoglycemia, sarcopenia, thyroid dysfunction, hypogonadotropic hypogonadism, bone disease, adrenal insufficiency, growth hormone dysfunction, and secondary hyperaldosteronism. The optimal tools for diagnosing diabetes and detecting hypoglycemia are the oral glucose tolerance test and continuous glucose monitoring system, respectively. Sarcopenia can be assessed through imaging and functional tests,

while other endocrine disorders are evaluated using hormonal assays and imaging studies. Treatment options include metformin, glucagon-like peptide-1 analogs, sodium-glucose co-transporter-2 inhibitors, and insulin, which are effective and safe for diabetes control. Established standards are followed for managing hypoglycemia, and hormone replacement therapy is often necessary for other endocrine dysfunctions. Liver transplantation can address some of these problems.

CONCLUSION

Liver cirrhosis leads to multiple endocrine disturbances, which can impact the patient's prognosis. Timely diagnosis and treatment are essential to reduce associated morbidity and mortality.

Key Words: Diabetes mellitus; Hypoglycemia; Thyroid diseases; Hypogonadism; Metabolic bone diseases; Liver cirrhosis

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Core Tip: This review explores hepatocrinology, the interplay between liver function and the endocrine system, focusing on endocrine disorders in liver cirrhosis. Cirrhosis triggers endocrine disorders like diabetes, hypoglycemia, sarcopenia, hepatic bone disease, secondary hyperaldosteronism, and thyroid, adrenal and growth hormone dysfunction. Diagnosis includes biochemical and hormonal assays and imaging studies. Treatment involves drugs like metformin, insulin, and hormone replacement therapies, while liver transplantation can alleviate certain conditions. Timely recognition and intervention are crucial for reducing associated morbidity and mortality in cirrhotic patients.

INTRODUCTION

⁵ Hepatocrinology is the field that investigates the bidirectional interaction between hepatic pathophysiology and the endocrine system^[1]. This relationship was established over 70 years ago when cases of gynecomastia and hypogonadism were documented in patients with Laennec's liver cirrhosis (LC). Pathological findings were also observed in their adrenal glands and pancreas^[2]. The liver synthesizes hormones and hormone-transporting proteins^[1] and plays a key role in the body's metabolic detoxification^[3]. Individuals with chronic liver diseases (CLD) often exhibit endocrinological disorders^[3,4]. Hepatic dysfunction can directly impact endocrine gland function due to toxin accumulation and indirectly affect protein synthesis and transport^[3].

LC, a consequence of hepatic inflammation and fibrosis, significantly contributes to morbidity and mortality in patients with CLD^[5]. It can lead to the development of hepatocellular carcinoma (HCC) and hepatic decompensation, characterized by manifestations such as ascites, hepatic encephalopathy, and bleeding from gastroesophageal varices^[5,6].

Despite its prognostic significance, the evaluation of endocrine pathologies in cirrhotic patients is often overlooked by specialists^[3,7,8]. Therefore, this manuscript aims to provide an updated narrative review on the epidemiology, pathophysiology, diagnosis, and treatment of endocrine disturbances in patients with LC.

LITERATURE REVIEW

¹ A narrative review was conducted through a bibliographic search in the PubMed/Medline, EMBASE, and Scielo databases, focusing on the search terms "hepatocrinology", "liver cirrhosis", "endocrine disturbances", "diabetes mellitus", "hypoglycemia", "sarcopenia", "thyroid dysfunction", "adrenal dysfunction", "hypogonadism", "hepatic bone disease", "secondary hyperaldosteronism", and "growth disorders". Systematic reviews, meta-analyses, clinical trials, narrative reviews, retrospective studies, cross-sectional studies, prospective studies, and case

reports were included, all closely aligned with the objectives of this manuscript. The search was limited to documents written in Spanish or English, excluding conference abstracts. Articles were not excluded based on their publication date. A total of 172 articles were included and are cited in the References section.

SEARCH RESULTS

LC ranks 15th in terms of disability-adjusted life years^[9]. In 2017, the global prevalence of compensated LC was estimated at 1395 cases per 100000 population, and for decompensated LC, it was 132 cases per 100000 population^[6], predominantly affecting males (60%)^[10]. LC accounts for 2.4% of global deaths, with approximately two-thirds of these cases occurring in men^[10]. Common causes of LC include hepatitis B and C infections, alcoholism, and non-alcoholic fatty liver disease (NAFLD)^[5,6]. Alcoholism is responsible for 60% of cirrhosis cases in regions such as Europe, North America, and Latin America^[9].

In early 2020, an international expert group introduced the metabolic dysfunction-associated fatty liver disease (MAFLD) definition, which offers a more inclusive approach than NAFLD. MAFLD identifies a broader range of patients with hepatic steatosis and high risks of metabolic disorders, including diverse causes of liver steatosis^[11,12]. Additionally, metabolic dysfunction-associated steatohepatitis (MASH) involves liver inflammation in the diagnosis^[13]. Upon examination of this updated definition, it is found that the prevalence of MAFLD accounts for approximately one-third of the global population^[14].

Around 80% of cirrhotic patients experience impaired glucose tolerance (IGT), and 20%-30% develop diabetes mellitus (DM)^[15,16]. Prevalence increases with the severity of hepatic dysfunction^[15,17] and is higher in cases secondary to MAFLD (56%), cryptogenic cirrhosis (51%), hepatitis C virus (32%), alcoholic cirrhosis (27%), and hepatitis B virus (22%)^[15]. Approximately half of cirrhotic patients develop hypoglycemia^[18]. Patients with both DM and LC have 2.7 times more episodes of hypoglycemia than those without LC. Risk factors include advanced age, renal impairment, and the use of

insulin, sulfonylureas, beta-blockers, or fibrates^[19]. Hypoglycemia is more common during concurrent infections and is associated with high mortality rates^[1,20]. Sarcopenia prevalence ranges from 30% to 70%, regardless of LC etiology, increasing with hepatic dysfunction severity and reaching 100% in liver transplant candidates^[21,22].

Thyroid dysfunction prevalence varies from 13% to 61% in cirrhotic patients^[23]. Osteoporosis affects 3%-43% of cirrhotic patients, particularly in the lumbar spine, femur, and hip^[23]. Adrenal insufficiency has been reported in 15%-72% of cirrhotic patients^[7]. This wide variability is possibly due to differences in clinical scenarios where these hormonal axes were studied. More than half of cirrhotic patients exhibit hypogonadism^[24].

PATHOPHYSIOLOGY

The liver produces insulin-like growth factor 1 (IGF-1) and betatrophin, influencing insulin sensitivity, angiotensinogen, contributing to blood pressure regulation, hepcidin, crucial in iron metabolism, and thrombopoietin, regulating platelet production. It also synthesizes hormone-transporting proteins such as IGF-binding protein (IGFBP), ⁵ sex hormone-binding globulin (SHBG), thyroid hormone-binding globulin (TBG), transthyretin, corticosteroid-binding globulin, and vitamin D-binding protein^[1].

LC, characterized by histological structural alterations, triggers distortion in hepatic angioarchitecture leading to portal hypertension. This results from an imbalance in intrahepatic circulation, favoring vasoconstriction due to increased vasoconstrictors compared to vasodilators, causing rapid changes in portal pressure^[5].

In LC, the production of nitric oxide, a vasodilator, decreases in sinusoidal endothelial cells, worsening intrahepatic vascular resistance and contributing to portal hypertension. This increase in intrahepatic vascular resistance elevates portal pressure, causing circulatory disturbances such as splanchnic arterial vasodilation^[5]. Splanchnic circulation contributes approximately 25% to systemic vascular resistance, so splanchnic vasodilation leads to a decrease in effective arterial blood volume. This triggers

systemic hypotension, inadequate arterial filling,²⁰ activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system (RAAS), and non-osmotic release of vasopressin, counteracting vasodilation by promoting salt and water retention, increasing plasma volume. Some of this excess plasma volume shifts to the peritoneal space, resulting in ascites^[5]. Figure 1A summarizes the pathophysiology of LC.

The described pathophysiological alterations lead to and/or are associated with multiple endocrine disorders, detailed below.

Diabetes mellitus

¹⁸ DM plays a significant role in the development of MAFLD and LC. DM associated with LC is known as hepatogenic diabetes^[17], and although its pathophysiology is not fully understood, it involves systemic insulin resistance due to alterations in adipokine secretion, proinflammatory cytokines, and free fatty acids^[1,25,26]. It also involves a decrease in non-oxidative disposal and oxidative metabolism of glucose, along with LC-induced sarcopenia^[27]. Hepatic insulin resistance is observed in cirrhotic patients with DM but not in those without DM^[16,17]. Gluconeogenesis is either maintained or decreased^[27]. Hyperinsulinemia is observed, more pronounced in hepatogenic diabetes, possibly due to reduced hepatic clearance caused by portosystemic shunting and hepatocyte dysfunction^[17]. However, it is unclear whether this hyperinsulinemia is a cause of insulin resistance or an adaptive response to it^[27].

Beta-cell dysfunction due to alcohol results from its direct toxic effect, while in hemochromatosis, damage originates from excessive iron accumulation in these cells. In the context of MAFLD, free fatty acids can deposit in pancreatic islets. Regarding hepatitis C virus infection, both direct damage through viral toxicity and indirect damage mediated by autoimmune responses can be observed^[27]. Decreased pancreatic beta-cell function is crucial in the transition to overt DM, suggesting that cirrhotic patients might benefit from interventions to protect or enhance the function of these cells, such as thiazolidinediones and incretin-based therapies^[17] (Figure 1B).

Hypoglycemia

Underlying mechanisms of hypoglycemia in LC include glycogen depletion, reduced gluconeogenesis, and alterations in insulin and other drug metabolism by the liver^[1,20], which is further diminished due to renal dysfunction associated with LC. Hypoalbuminemia and fluid retention increase the free fraction of drugs^[28].

Patients with HCC may experience hypoglycemia due to a syndrome known as non-islet cell tumor hypoglycemia. This syndrome is characterized by decreased serum levels of insulin, C-peptide, and beta-hydroxybutyrate, along with increased levels of IGF-2 and the IGF-2/IGF-1 ratio^[29-31] (Figure 1B).

Sarcopenia

Sarcopenia is a syndrome of muscle loss, the definition of which in LC is still debated. Its pathophysiology in this context involves multiple factors, including reduced protein synthesis due to decreased intake, hypercatabolism, and increased energy expenditure. Chronic depletion of hepatic glycogen leads to the search for alternative substrates for energy production, such as fatty acids and benefits of branched-chain amino acid (BCAA), especially during prolonged fasting states like sleep, as these patients experience a state of 'accelerated fasting', a deteriorated adaptive response in which gluconeogenesis, fat oxidation, and ketogenesis rates increase^[21,32]. Hepatic encephalopathy leads to physical inactivity and, additionally, hyperammonemia and increased production of myostatin, a member of the transforming growth factor β superfamily that inhibits muscle protein synthesis and increases its degradation^[21,32]. Alcohol decreases ureagenesis and contributes to hyperammonemia, in addition to its direct toxic effects on muscles^[22]. Insulin resistance, common in LC and MAFLD, leads to decreased protein synthesis, increased catabolism, and lipotoxicity^[21]. Testosterone and growth hormone (GH)/IGF-1 normally stimulate protein synthesis and suppress myostatin production, but their decrease in LC contributes to sarcopenia^[22,32].

Myosteatosis is the pathological accumulation of fat in skeletal muscles and affects half of cirrhotic patients, worsening with age and liver dysfunction progression. In addition to sarcopenia, it holds significant prognostic importance^[22] (Figure 1B).

Hypogonadotropic hypogonadism

LC can lead to hypogonadotropic hypogonadism. In males, the main clinical manifestation is gynecomastia, although decreased libido, hair loss, sarcopenia, obesity, and fatigue can also occur. In females, common menstrual irregularities include oligomenorrhea or amenorrhea^[1,24].

In males, this condition is due to hyperestrogenism caused by reduced hepatic clearance of estrogen due to portal hypertension, decreased testosterone production, increased SHBG levels, and hypothalamic-pituitary dysfunction^[1,24]. The increase in SHBG levels is likely due to enhanced hepatic production, hyperstimulated by hyperestrogenism and lacking suppression due to lower testosterone levels. The reduction in free testosterone is even greater since the existing testosterone binds strongly to SHBG^[33]. In females, the primary mechanism is hypothalamic-pituitary dysfunction^[1,24].

Except for LC caused by alcohol, suppressed or inappropriately normal levels of gonadotropins are observed, which might reverse after liver transplantation^[1,24]. Other involved mechanisms include LC-induced hyperprolactinemia, inhibiting gonadotropins, and IGF-1 deficiency, which also contributes to hypogonadism^[23] (Figure 1B).

Thyroid dysfunction

The liver is the primary organ where the conversion of thyroxine to its active form, triiodothyronine, occurs through type 1 deiodinase, making LC commonly associated with thyroid hormone dysfunction^[23]. Furthermore, thyroid hormones regulate hepatocyte metabolic rate. Hepatic dysfunction can affect thyroid function and vice

versa^[34]. A higher frequency of hypothyroidism and euthyroid sick syndrome, and to a lesser extent, cases of hyperthyroidism, have been observed^[23].

¹⁴ Hypothyroidism is associated with dyslipidemia and a higher body mass index (BMI), increasing the risk of MAFLD. Reduced thyroid hormones decrease intrahepatic lipolysis and triglyceride clearance; they also increase tumor necrosis factor α (TNF- α) and leptin while decreasing adiponectin, thus contributing to hepatic inflammation and fibrosis^[35].

¹¹ Thyroid autoimmunity is often found in patients with autoimmune liver diseases such as autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis^[1,36].

Hyperthyroidism can cause liver dysfunction due to prolonged exposure to elevated thyroid hormone levels, leading to direct hepatic toxicity and hepatic necrosis due to right-sided heart failure caused by longstanding thyrotoxicosis^[35].

Additionally, an increase in serum TBG concentration has been observed in HCC, normalizing after tumor resection^[1] (Figure 1B).

Hepatic bone disease

LC often leads to disturbances in bone metabolism, such as osteoporosis, and less frequently, osteomalacia or rickets. These effects result from a combination of factors, including nutritional deficiencies, the proinflammatory state, and hypogonadism^[23]. Vitamin D levels are inversely associated with the degree of hepatic dysfunction, overall mortality, and infections in cirrhotic patients, as well as the severity and prognosis in HCC^[37,38]. Decreased IGF-1 production contributes to reduced bone turnover and bone mass loss^[1,39,40] (Figure 1B).

Adrenal insufficiency

Adrenal insufficiency has been observed in cirrhotic patients, especially in situations of septic shock or hepatic decompensation, known as hepato-adrenal syndrome^[41]. This phenomenon has also been described in critically ill cirrhotic patients, with or without

sepsis, as well as in liver transplant recipients and even some stable patients^[42,43]. The exact mechanism of this phenomenon is not yet fully understood; however, it has been suggested that the reduction in hepatic transport of cholesterol through high-density lipoproteins (HDL), due to decreased levels of apolipoprotein A1 and enzymatic activity of lecithin-cholesterol acyltransferase, could reduce the available substrates for steroid synthesis in the adrenal cortex^[1,7,44]. This, in turn, could result in the adrenal glands' inability to produce adequate amounts of cortisol, especially in stressful situations, leading to adrenal insufficiency^[42]. Additionally, other possible mechanisms have been suggested, such as chronic hypoperfusion of the adrenal glands due to splanchnic vasodilation and the impact of proinflammatory cytokines such as interleukin 1 (IL-1), IL-6, and TNF- α , which tend to increase in LC and could suppress both corticotropin-releasing hormone and adrenocorticotrophic hormone secretion, as well as reduce peripheral tissues' sensitivity to glucocorticoids^[7,23,42] (Figure 1B).

Growth hormone dysfunction

IGF-1 and IGFBP are mainly synthesized in the liver and play a fundamental role in regulating cellular growth and differentiation^[23]. GH stimulates the production of IGF-1 in the liver, essential for growth and development in childhood and the maintenance of cardiovascular health in adults^[23]. The actions of IGF-1 are locally and systemically regulated by IGFBP. In LC, GH levels increase due to a heightened response to GH-releasing hormone, but hepatic synthesis capacity of IGF-1 decreases due to reduced hepatic mass, fewer GH receptors in the cirrhotic liver, and blockade exerted by certain IGFBP^[1,23]. Consequently, the negative feedback exerted by IGF-1 diminishes, leading to further elevation of GH levels^[23].

Linear growth in children with LC is often restricted despite elevated GH levels, due to GH resistance caused by reduced hepatic synthesis of IGF-1 and IGFBP-3^[45] (Figure 1B).

Secondary hyperaldosteronism

Splanchnic vasodilation in LC leads to a decrease in effective arterial blood volume, stimulating the RAAS, the ² sympathetic nervous system, and arginine-vasopressin, causing retention of sodium and water. Angiotensin II induces systemic arterial vasoconstriction, stimulates vasopressin release, maximizes sodium (and water) reabsorption, and strongly activates the sympathetic nervous system. Besides its effects on sodium retention and blood pressure elevation, ² aldosterone activates mineralocorticoid receptors in non-epithelial tissues. In the presence of high sodium intake, it causes oxidative stress, endothelial dysfunction, inflammation, fibrosis, and remodeling, leading to cardiovascular and renal injuries. Additionally, it can lead to peripheral insulin resistance and metabolic syndrome^[46-48] (Figure 1B).

DIAGNOSIS

Within the diagnosis of LC, it is crucial to assess the disease stage, quantify hepatic fibrosis, identify the presence of portal hypertension, and determine underlying causes. Although liver biopsy remains the gold standard, non-invasive tests such as the Fibrosis-4 Index and hepatic elastography can be utilized to evaluate the degree of fibrosis, with elastography being a practical choice^[5].

The Child-Pugh classification stands as one of the most widely used methods for evaluating the prognosis in cirrhotic patients. It categorizes patients into three groups with varying survival prognoses. We use the term “compensated cirrhosis” to refer to Child-Pugh class A, encompassing patients with normal liver function and those with mildly impaired liver function (slight elevation in serum bilirubin or prothrombin time, or a history of decompensation such as ascites, jaundice, variceal bleeding, hepatorenal syndrome, or encephalopathy). The term “decompensated cirrhosis” refers to Child-Pugh classes B and C, including patients with moderate or severe impairment in liver function, presence of ascites and/or encephalopathy, and a history of decompensation^[49,50].

For the study of endocrine disorders associated with LC, relevant biochemical and hormonal tests are required, as explained below, and summarized in Figure 2.

Diabetes mellitus

Fasting plasma glucose (FPG) measurement is economical but demands specific conditions for accuracy. The optimal threshold for diagnosing DM in patients with CLD has not been defined, as traditional cutoffs have reduced sensitivity in these patients. For instance, in patients with LC due to hepatitis C, a FPG level of 5.94 mmol/L (107 mg/dL) might be considered diagnostic of DM, although it remains uncertain if this cutoff could apply to LC from other etiologies^[51,52]. In patients with LC and DM, FPG levels are often normal or low due to alterations in hepatic gluconeogenesis^[25,28,50,51]. The 75 g oral glucose tolerance test (OGTT) can diagnose IGT and identify more cases of DM^[52].

Hemoglobin A1c (HbA1c) is commonly used in DM but is inaccurate in cirrhotic patients due to factors such as reduced red blood cell lifespan from hypersplenism, anemia, gastrointestinal bleeding, or vitamin deficiency. In patients with LC and DM, the average HbA1c reported is 39 mmol/mol (5.7%)^[25,28,50,51,53].

Hepatogenic diabetes distinguishes itself from type 2 DM by its weaker association with traditional risk factors and complications. FPG levels and HbA1c are normal. Diagnosis requires an abnormal result on the 75-g OGTT^[17].

The most suitable method for monitoring blood glucose in cirrhotic patients with DM is controversial. Continuous glucose monitoring (CGM) has proven more accurate than HbA1c measurement in these patients^[53]. Glycated albumin and fructosamine reflect glycemic control over the last 2 wk to 3 wk, but their accuracy decreases in LC due to altered protein metabolism. Corrections have been proposed but lack validation^[52]. CGM has also been found superior to fructosamine measurement in cirrhotic patients^[53]. Serum 1,5-anhydroglucitol is a sensitive glycemic marker in patients with DM, but its accuracy decreases in LC due to altered metabolism and malnutrition^[52]. Capillary blood glucose monitoring is a suitable alternative for glycemic monitoring, and it's recommended to perform it at different times of the day, including nighttime

and early morning, as up to 20% of patients with HbA1c below 7% experience nocturnal hypoglycemia^[50].

On the other hand, some cirrhotic patients might suffer from pancreatic diabetes, characterized by concurrent exocrine pancreatic insufficiency within the context of chronic pancreatitis triggered by chronic alcoholism, a contributing factor to LC. This condition can be diagnosed through fecal elastase 1 testing^[50,54].

Hypoglycemia

The Endocrine Society recommends investigating hypoglycemia when the Whipple triad is present (neuroglycopenic and autonomic symptoms of hypoglycemia, evidence of low blood glucose, and symptom resolution upon glucose elevation). In healthy individuals, symptoms of hypoglycemia manifest when blood glucose is below 3.05 mmol/L (55.00 mg/dL). However, in cases of recurrent hypoglycemia, the thresholds for symptoms can be lower. Hypoglycemia in people without DM is rare and can be caused by critical illnesses such as renal, hepatic, or cardiac failure^[55]. For people with DM, the American Diabetes Association defines hypoglycemia as a glucose concentration below 3.89 mmol/L (70.00 mg/dL)^[56]. A study in patients with chronic or acute hepatic failure defining hypoglycemia as blood glucose below 2.80 mmol/L (50.40 mg/dL) demonstrated that half of the patients experienced a hypoglycemic episode during their hospitalization, establishing it as an independent risk factor for 90-d mortality (OR = 8.72, $P = 0.01$)^[57]. Another study in hospitalized cirrhotic patients found an association between hypoglycemia and positive blood cultures ($P = 0.01$), also serving as a predictor for bacteremia and mortality. Seventy-five percent of the patients in this study had compensated LC, suggesting that alterations in hepatic gluconeogenesis could exist and be clinically relevant in early stages of liver disease^[58].

Up to 8% of cirrhotic patients have been reported to experience silent hypoglycemia, which could lead to permanent brain damage, highlighting the need for regular glucose monitoring^[19]. In high-risk hospitalized patients with DM, including those with hepatic

dysfunction, CGM is recommended for the rapid detection of nocturnal hypoglycemia^[59].

Sarcopenia

Muscle mass can be assessed using ⁵ magnetic resonance imaging or computed tomography (CT), which are currently considered the gold standard, enabling the diagnosis of both sarcopenia and myosteatorsis^[22]. CT measures the cross-sectional area of abdominal skeletal muscles at the level of the third lumbar vertebra, making it the most used modality with validated specific cutoff points by gender ($< 50 \text{ cm}^2/\text{m}^2$ in men and $< 39 \text{ cm}^2/\text{m}^2$ in women, generally). However, its cost and repeated exposure to radiation may limit its use^[22,60]. Dual-energy X-ray absorptiometry (DXA) is another current gold standard, although its utility is limited in the presence of edema^[22]. Electrical bioimpedance is also a useful tool, albeit constrained by its high cost and the presence of edema^[21,22]. Less commonly used methods include mid-arm muscle circumference and quadriceps ultrasound^[21]. Anthropometric assessments, such as skinfold measurements and BMI, can be helpful in the context of compensated LC but are much less reliable in cases of more severe liver dysfunction. On the other hand, the combination of anthropometry and ultrasound assessment of thigh muscle thickness has shown significant correlation with CT results, offering a useful and less expensive approach^[22].

Muscle strength can be evaluated by measuring handgrip strength, which also allows for the detection of reduced strength (⁵ defined as handgrip strength $< 27 \text{ kg}$ in men and $< 16 \text{ kg}$ in women) in the context of concurrent myosteatorsis, where there might be an increase in muscle volume at the expense of fat infiltration^[22,60].

Hypogonadotropic hypogonadism

In patients with LC, hypogonadism affects reproductive and sexual function, leading to a negative impact on their quality of life^[24].

In clinical practice, having objective tools to assess the presence and severity of erectile dysfunction in patients is useful, such as the International Index of Erectile Function (IIEF)^[61], and its short version, the IIEF-5, which addresses erectile and orgasmic function, sexual desire, as well as sexual intercourse and overall satisfaction^[62]. The Female Sexual Function Index (FSFI) covers domains such as desire, arousal, lubrication, orgasm, satisfaction, and pain^[63].

In males, the initial evaluation should include testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), and SHBG. When interpreting results, it is important to consider that in patients with LC, SHBG production is altered, and the reference ranges for testosterone depend on the assay platforms used for androgen measurement^[24]. A low total or low-normal testosterone level in the context of symptoms of reproductive dysfunction or sexual dysfunction requires further evaluation with measurement of free or bioavailable testosterone and concurrent LH and FSH values. Testosterone concentrations vary throughout the day and from day to day, so total testosterone concentrations should be measured in fasting samples on different mornings. In cases of SHBG alteration, such as in LC, or when the initial total testosterone concentration is close to the lower limit of the normal range, free testosterone concentrations should be determined. The lower limit of the normal range for total testosterone in young, non-obese, healthy men is 9.2 nmol/L (264 ng/dL). A harmonized reference range for free testosterone has not yet been established, so laboratory-specific lower limits can be utilized. Once hypogonadism is documented, LH and FSH tests should be requested. Elevated values suggest primary hypogonadism, whereas low or inappropriately normal values indicate secondary (hypogonadotropic) hypogonadism^[64].

In females, the initial approach should include FSH, LH, PRL, and thyroid-stimulating hormone (TSH). Ideally, FSH and LH should be measured on the second or third day of the menstrual cycle; however, this is often not possible due to the presence of oligomenorrhea or amenorrhea^[65]. Elevated PRL levels require further investigation, while abnormal TSH indicates thyroid dysfunction. Elevated LH and FSH

concentrations suggest primary ovarian insufficiency, whereas ³ low or normal levels in the presence of irregular menstruation are more consistent with hypothalamic or pituitary pathology (hypogonadotropic hypogonadism)^[24,66].

Thyroid dysfunction

Thyroid dysfunction is associated with abnormalities in liver enzymes and should be ruled out in cases of unknown elevation^[34]. Regular thyroid function tests are necessary for patients with cirrhosis, including measurements of TSH, free thyroxine, and free triiodothyronine (FT3)^[67].

Hypothyroidism: Clinical manifestations of hypothyroidism are nonspecific and can mimic a state of liver dysfunction with symptoms such as fatigue, myalgias, cramps, dyspnea, and edema. It may rarely present with ascites or mimic hepatic encephalopathy in cirrhotic patients. Hypothyroidism should be suspected and ruled out in patients with LC and seemingly refractory hepatic encephalopathy treatment^[68]. Primary hypothyroidism is often associated with a moderate elevation of liver enzymes^[69]. These abnormalities usually normalize after hormonal replacement therapy with levothyroxine^[34]. Histology is usually normal; however, the relationship between hypothyroidism and liver fibrosis has been evaluated compared to euthyroidism, showing a 2.48 times higher risk^[70].

Subclinical and overt hypothyroidism present nonspecific symptoms. Hypothyroidism has been associated with a 61% increased risk of progression to MASH in patients with MAFLD^[71].

Euthyroid sick syndrome: This clinical entity is characterized by low FT3 and normal or low TSH concentration. These alterations usually occur in critically ill patients, approximately 70% of those admitted to the intensive care unit and have been associated with increased mortality^[72]. This syndrome lacks clinical manifestations or characteristic physical exam findings. However, it should be noted that it can affect

patients with preexisting thyroid diseases, and the use of certain drugs in these critically ill patients can alter thyroid hormone secretion^[73]. FT3 inclusion in mortality prediction scales for patients with liver failure, such as the FT3-MELD score, performs better in short-term mortality prediction^[74].

Hyperthyroidism: The liver is a significant target of excess thyroid hormones, reflected in the fact that 15%-76% of newly diagnosed hyperthyroid patients exhibit abnormal liver function tests^[67]. The most common abnormalities in patients with thyrotoxicosis are elevated alkaline phosphatase (64%), gamma-glutamyl transferase (62%), alanine aminotransferase (37%), and aspartate aminotransferase (27%)^[67]. Histologically, patients with hyperthyroidism may present with mild liver injury, with centrolobular cholestasis; however, progression of damage is rare and normalizes with treatment^[34]. Liver involvement in overt hyperthyroidism is usually self-limiting, although there are reported cases of patients with thyrotoxicosis and fulminant liver failure, especially if coexisting with heart failure or in cases of thyroid storm. Thyrotoxicosis should be considered in the differential diagnosis of causes of acute liver failure, especially in patients with known thyroid dysfunction history^[75].

Hepatic bone disease

Bone disease is one of the primary complications of LC and can result in fractures spontaneously or following low-intensity traumas, increasing morbidity and decreasing the quality of life. The prevalence of osteoporosis in cirrhotic patients varies according to the cause, being higher in cases secondary to cholestatic disease, ranging between 20%-44%^[76,77]. Regarding the distribution of alterations in bone mineral density (BMD), it has been observed that abnormalities are more common in the lumbar spine, with no differences at the hip level^[78]. DXA is considered the method to measure BMD and diagnose osteoporosis in cirrhotic patients. However, BMD assessment cannot fully predict or explain the risk of increased fractures, making it necessary to use complementary diagnostic tools such as quantitative CT^[78]. A quantitative tomographic

analysis with a finding of BMD below 80 mg/cm^3 diagnoses osteoporosis^[79]. Within the findings in bone microstructure, it has been found that the trabecular bone fraction and trabecular thickness were reduced in advanced cholestatic liver disease^[80]. Cirrhotic patients have been found to have lower trabecular bone volume, lower cortical BMD in the tibia, and lower Z scores in the lumbar spine and hip^[78].

Due to these findings and the alterations in calcium and vitamin D metabolism that can occur in patients with liver injury, DXA is recommended when the diagnosis of LC is confirmed and then repeated every two or three years^[81]. Also, since ascites can cause an underestimation of BMD, increasing values by up to 4.2%-7.0% after paracentesis, measuring BMD immediately after paracentesis is recommended. Additionally, a lateral X-ray of the dorsal and lumbar spine segments or vertebral morphometry by DXA should be performed to look for vertebral fractures^[77]. Ideally, BMD measurement should be done with the trabecular bone score, which can help identify cirrhotic patients at high risk of vertebral fractures^[82].

In LC, vitamin D requirements might increase, so its levels should be measured, along with serum calcium, serum phosphorus, and urinary calcium^[81]. The optimal vitamin D levels are controversial. Most authors suggest that optimal levels are between 74.88 nmol/L and 124.80 nmol/L ($30\text{-}50 \text{ ng/mL}$), while levels from 49.92 nmol/L to 74.88 nmol/L ($20\text{-}30 \text{ ng/mL}$) are considered insufficient. Below 49.92 nmol/L (20 ng/mL) is classified as vitamin D deficiency, and below 24.96 nmol/L (10 ng/mL) is considered severe deficiency^[38].

Adrenal insufficiency

Adrenal insufficiency in cirrhotic patients is a common but underdiagnosed problem due to its clinical presentation similarity with stress-induced adrenal insufficiency and the challenge of finding an appropriate diagnostic method to evaluate the hypothalamic-pituitary-adrenal axis in patients with evident decreased synthesis of albumin and corticosteroid-binding globulin. As described in the pathophysiology, this decreased synthesis is the main mechanism causing this disorder^[7,83,84].

Ninety percent of cortisol is bound to transport proteins synthesized by the liver, so as hepatic function deteriorates, the prevalence of adrenal insufficiency increases^[7,85,86]. The prevalence of adrenal insufficiency in non-hospitalized patients ranges from 26%-49%, and in hospitalized patients, it ranges from 51%-82%. Moreover, in Child-Pugh class A patients, the prevalence of adrenal insufficiency is 0%-44%, in Child-Pugh class B patients, it is 23%-54%, and in Child-Pugh class C patients, it is 57%-68%. Therefore, its evaluation is of vital importance in critically ill patients and in advanced stages of hepatic dysfunction^[7,84-87].

Despite the lack of a consensus, the presence of adrenal insufficiency should be evaluated in patients with refractory hypotension, patients with sodium levels less than 125 mmol/L, and patients with HDL levels less than 0.39 mmol/L (15 mg/dL)^[85,88-90].

In non-cirrhotic patients, adrenal insufficiency is diagnosed by an inadequate response to the standard 250 µg ACTH stimulation, defined as a maximum total cortisol level of 496.62 nmol/L (18 µg/dL). Additionally, the cortisol delta less than 248.31 nmol/L (9 µg/dL) in critically ill patients or the total cortisol level at 8 a.m. lower than 137.95 nmol/L (5 µg/dL) is routinely used. The decrease in protein synthesis in cirrhotic patients complicates the use of these diagnostic methods. Therefore, only the measurement of free plasma cortisol or salivary cortisol can be used, and these should be measured in parallel with total cortisol to assess probable deficiency, with an average delay of 1 wk to 2 wk and limited availability in emergency services. Based on the above, we suggest measuring these in situations where the patient's clinical condition raises doubts about the diagnosis^[83,87,91].

Growth hormone dysfunction

In patients at high risk of complications such as hypoglycemia, measuring IGF-1 levels below normal limits is often sufficient. However, the standard diagnosis is defined by a maximum GH response to hypoglycemia below 3 µg/L (3 ng/mL)^[85,92-96]. However, this test can lead to severe hypoglycemia, need close supervision, and is contraindicated in some patients. The macimorelin stimulation test has become the gold standard for

diagnosis of GH deficiency^[97], however, there is no data regarding its performance in patients with LC.

Secondary hyperaldosteronism

Patients may be asymptomatic or present with new or resistant hypertension, fatigue, headache, polyuria, and polydipsia. Hypokalemia, mild hypernatremia, and mild hypermagnesemia are often found^[47,48,98].

Plasma renin concentration and plasma renin activity (PRA) levels are part of the initial diagnostic approach and are elevated, unlike in primary hyperaldosteronism. Plasma aldosterone concentration (PAC) is also elevated, as well as the PAC/PRA ratio, although not at the levels observed in primary hyperaldosteronism [PAC > 0.554 nmol/L (20 ng/dL) and PAC/PRA > 30]^[47,48,98].

Confirmation of the diagnosis of hyperaldosteronism involves aldosterone suppression, often through a 3-d oral sodium load (5000 mg of sodium in the diet or 90 mEq of sodium in tablets) followed by aldosterone measurements in urine. A value above 33.29 nmol/d (12 µg/d) confirms the diagnosis. Intravenous infusion of 2 L of isotonic saline over 4 h is an alternative, requiring a PAC value that exceeds 0.277 nmol/L (10 ng/dL) to confirm the diagnosis, although it has a 30% false negative rate^[47,48].

TREATMENT

Diabetes mellitus

The goals of DM management in cirrhotic patients vary based on the presence of decompensation. For compensated patients, it is recommended to maintain the targets set by the American Diabetes Association: FPG between 4.44 and 7.22 mmol/L (80-130 mg/dL) and postprandial glucose less than 9.99 mmol/L (180 mg/dL). However, in decompensated cirrhotic patients, considering the decreased survival associated with cirrhosis complications, more flexible objectives are proposed: FPG between 5 and 8.32

mmol/L (90-150 mg/dL), postprandial glucose less than 11.1 mmol/L (200 mg/dL), and pre-meal glucose levels between 5.55 and 11.1 mmol/L (100-200 mg/dL)^[28,50].

Regarding physical activity, a regimen of 150 to 300 min of intense physical activity per week, divided between aerobic exercises and resistance training, is recommended^[28,99]. Alcohol cessation can aid in weight control. Additionally, following a Mediterranean diet pattern with 50%-65% of carbohydrates is advised to prevent hypoglycemia^[100].

Metformin, with its short half-life and renal elimination, improves insulin resistance and carries a low risk of hypoglycemia. In patients with compensated LC, it can be used as a first-line medication, given the findings suggesting a reduced risk of HCC^[25,28,50]. A study showed that metformin use in diabetic patients was associated with reduced mortality [Hazard ratio (HR): 0.68, 95% confidence interval (95%CI): 0.61-0.75], although not with rates of HCC or hepatic decompensation^[101]. Other studies have confirmed reduced mortality^[102] and demonstrated a decrease in the risk of decompensation^[103] and progression to HCC^[104-106]. Metformin is often avoided in patients with liver diseases due to concerns about lactic acidosis. However, metformin is not inherently hepatotoxic, and metformin-associated lactic acidosis is extremely rare, with an incidence of fewer than 10 per 100000 patient-years of exposure in patients without renal insufficiency^[52,107,108]. It is recommended to use a maximum of 1500 mg/d of metformin in cirrhotic patients and to avoid it entirely in contexts of hypoxemia, dehydration, sepsis, or decompensated cirrhosis^[50,109].

The metabolism and duration of action of sulfonylureas vary. Long-acting ones like glyburide and glimepiride may pose a higher risk of hypoglycemia, especially in patients with renal impairment, compared to other sulfonylureas like glipizide^[100]. A study revealed that sulfonylureas were associated with a reduced risk of major cardiovascular events (aHR: 0.69, 95%CI: 0.61-0.80), stroke (aHR: 0.66, 95%CI: 0.53-0.83), ischemic heart disease (aHR: 0.66, 95%CI: 0.53-0.83), and heart failure (aHR: 0.71, 95%CI: 0.55-0.92), with no significant differences in severe hypoglycemia risk (aHR: 0.78, 95%CI: 0.52-1.10)^[110]. This study was conducted in compensated cirrhotic patients,

suggesting the cautious use of sulfonylureas in these cases but in lower doses than usual to prevent hypoglycemia^[28,50,100]. However, they are contraindicated in decompensated LC^[109].

Regarding meglitinides, there are no specific guidelines available. However, they might serve as an alternative to sulfonylureas, although repaglinide should be avoided due to its lower clearance and potential hepatotoxicity^[28,50]. Nateglinide can be used in Child-Pugh A and B patients, with doses lower than usual to prevent hypoglycemia^[50].

Thiazolidinediones are insulin sensitizers useful in the treatment of MAFLD and MASH^[52]. A meta-analysis demonstrated that pioglitazone improves advanced fibrosis but with a high prevalence of side effects such as weight gain and lower extremity edema^[111]. They have shown normalization of liver enzymes in patients with MASH, along with reduced hepatocellular lesions, parenchymal inflammation, and fibrosis^[52]. They can cause dose-dependent weight gain^[112,113]. Conversely, a study showed that the rate of major vascular events for thiazolidinedione users was higher, with aHR of 1.81 (1.28-2.55) for stroke, 1.59 (1.03-2.44) for coronary artery disease, and 2.09 (1.22-3.60) for heart failure, with rosiglitazone posing a higher risk than pioglitazone^[114]. Hence, careful use is recommended, and they should be avoided in decompensated cirrhotic patients^[28,50]. Pioglitazone can be cautiously used in patients with LC, suitable for those classified as Child-Pugh class A, but it ¹⁷should be avoided if liver enzymes exceed ¹⁷three times the upper limit of the normal range and in patients of classes B and C^[50,109]. Rosiglitazone is associated with adverse cardiovascular effects in DM and cirrhotic patients^[28].

Dipeptidyl peptidase-4 inhibitors (DPP-4i) prevent the inactivation of ¹³glucagon-like peptide 1 (GLP-1) primarily ¹³and gastric inhibitory polypeptide (GIP), ensuring glycemic control without the risk of hypoglycemia, weight gain, or reduction in muscle mass^[28]. Their use has been associated with major episodes of liver decompensation (¹⁶aHR: 1.35, 95%CI: 1.03-1.77), variceal bleeding (aHR: 1.67, 95%CI: 1.11-2.52), and liver failure (aHR: 1.35, 95%CI: 1.02-1.79), although without a significant increase in mortality^[115]. Vildagliptin carries a high risk of hepatotoxicity, while other DPP-4i can be used in

Child-Pugh A cirrhotic patients without dose adjustment. Caution is required in Child-Pugh B patients, and they are not recommended for Child-Pugh C patients^[50,109]. Except for linagliptin, DPP-4i are eliminated *via* renal excretion^[28], necessitating dose adjustment in renal dysfunction^[25].

GLP-1 receptor agonists (GLP-1 RA) offer various beneficial effects in patients with DM, such as improved insulin sensitivity in adipose and hepatic tissues, inhibition of glucagon secretion, increased satiety, delayed gastric emptying, weight loss, and reduced hepatic lipogenesis. They improve glycemia without the risk of hypoglycemia as they stimulate insulin production in a glucose-dependent manner^[28]. Studies have shown that GLP-1 RA use is associated with a lower risk of mortality (aHR: 0.47, 95%CI: 0.32-0.69), cardiovascular events (aHR: 0.60, 95%CI: 0.41-0.87), and decompensated LC (aHR: 0.70, 95%CI: 0.49-0.99)^[116]. GLP-1 RA has been linked to a lower rate of hepatic decompensations compared to DPP-4i use (105.2 *vs* 144.0 per 1000 person-years) and a lower rate of ascites and variceal bleeding. Similar results were found when comparing GLP-1 RA with sulfonylureas. No significant differences were observed in the rate of hepatic decompensations when comparing GLP-1 RA with sodium-glucose cotransporter 2 inhibitors (SGLT-2i)^[117]. In patients at high risk of sarcopenia, closer monitoring is recommended due to GLP-1 RA-induced weight loss, which may include lean mass loss^[118]. Liraglutide and semaglutide have shown effectiveness in improving NASH^[119,120]. GLP-1 RA undergoes no hepatic metabolism, enabling their use without dose adjustment in Child-Pugh A cirrhotic patients. Consideration might be given to their cautious use in class B patients. However, due to limited data in patients with liver insufficiency, their use should be avoided in class C patients^[50,109]. The dual GLP-1 and GIP agonist (tirzepatide) has been shown to improve MAFLD and MASH^[121-123], and the triple GLP-1, GIP, and glucagon agonist (retatrutide) has similar effects in animal models^[124,125], although their effects in managing DM in patients with LC remain unknown.

SGLT-2i act in the proximal tubule of the nephron, increasing urinary glucose and sodium excretion^[28]. Apart from reducing glycemia and providing cardiovascular and

7
renal benefits^[126], they have been reported to improve aminotransferase levels and hepatic steatosis in patients with DM and MAFLD^[127,128]. SGLT-2i are comparable in efficacy to GLP-1 RA in reducing hepatic decompensations^[117]. A study found that the use of SGLT-2i in cirrhotic patients prevents worsening liver function and hepatic fibrosis^[129]. There are also case reports where the addition of SGLT-2i controlled ascites, hydrothorax, and peripheral edema^[130]. These effects are akin to loop diuretics^[131], but more studies are needed to confirm their safety and efficacy^[132]. Inhibition of renal sodium reabsorption could ameliorate the LC-associated RAAS dysfunction, thus reducing renin secretion; however, this hypothesis requires further confirmation in additional studies^[133]. 10
SGLT-2 inhibitors are safe in Child-Pugh A patients; however, caution is required when using them in class B patients and they should be avoided in class C due to the risk of dehydration and hypotension associated with their use. Lower doses should be considered when initiating treatment in cirrhotic patients^[28,109].

Alpha-glucosidase inhibitors, such as acarbose, interfere with gastrointestinal carbohydrate absorption, reducing postprandial hyperglycemia. This mechanism is relevant in cirrhotic patients due to their impaired splanchnic and peripheral glucose uptake, making them susceptible to postprandial hyperglycemia^[28]. Another potential advantage of this drug is its effect on hepatic encephalopathy by decreasing proteolytic flora, which elevates blood ammonia levels, and its associated laxative effect^[28,50]. 10
Alpha-glucosidase inhibitors are relatively safe and can be used without dose modification in Child-Pugh class A and B patients, but they are not recommended in class C patients. They are also not recommended in cases of poorly controlled DM due to their insufficient hypoglycemic effectiveness^[50,109].

Approximately 40%-50% of endogenously produced insulin is metabolized in the liver. Despite this, insulin therapy remains the most effective treatment for patients with LC, albeit with the caution of an increased risk of hypoglycemia. In cirrhotic patients with compensated DM, insulin therapy is suggested for those unable to use oral medications, those with inadequate glycemic control [FPG above 16.65 mmol/L (300 mg/dL) or HbA1c above 86mmol/mol (10%)], or in conditions such as sepsis,

encephalopathy, bleeding, or acute kidney injury. Insulin is the preferred choice for patients with DM and decompensated LC^[28]. It's important to note that during LC decompensations, hepatic insulin metabolism is further reduced, potentially decreasing the need for insulin, necessitating close glucose monitoring^[109,134].

Sliding scale-based insulin therapy is not recommended. Ideally, insulin regimens should include a basal insulin to control overnight and fasting glucose. Long-acting insulin analogs such as glargine, detemir, degludec, or neutral protamine lispro (NPL) are preferred^[28]. Glargine and degludec have a duration of action of approximately 24 h, while detemir duration is shorter. Glargine and detemir cannot be mixed with fast-acting insulins due to altered kinetics, but degludec can. NPL's activity is similar to neutral protamine Hagedorn insulin, with slightly higher hypoglycemia risk than the others^[28].

Given the frequent postprandial hyperglycemia in cirrhotic patients, fast-acting insulins are often added. Rapid-acting insulin analogs (lispro, aspart, or glulisine) or regular short-acting human insulin can be used to cover additional insulin needs^[28]. Gentile and colleagues conducted a 12-wk study involving 50 patients who received comparable doses of insulin lispro and regular insulin before meals, in addition to insulin glargine. The study found that pre-meal blood glucose levels were similar between the lispro and regular insulin groups. However, the increase in blood glucose levels at one and two hours after meals was significantly higher in patients treated with regular insulin, with a difference of 2.22 mmol/L (40 mg/dL) at two hours. Furthermore, patients using regular insulin experienced greater reductions in glucose levels at 3 h and 4 h after meals and during the night. After two weeks, the incidence of hypoglycemia was significantly higher in patients using regular insulin compared to lispro (9.7 vs 1.8, $P < 0.001$). Consequently, the study recommended insulin lispro due to its superior safety profile in managing postprandial hyperglycemia^[135].

In patients with CLD, it is recommended to reduce insulin dosage by 25% and advise patients about the risk of hypoglycemia^[28]. Initiation of insulin therapy is advised at a dose of 0.1-0.2 IU/kg/d, potentially increased if blood glucose levels are significantly

elevated. Subsequent doses can be adjusted based on glucose levels, with a recommended increase of 2 units every 3 d if glucose remains above the desired range. Additionally, the addition of rapid-acting insulin can be considered if glycemic goals are not met, ideally starting at 4 units or 10% of the basal insulin, increasing by 1-2 units every 3-4 d^[28]. Insulin dosing should be titrated as needed, and the use of insulin analogs is preferred to reduce the risk of hypoglycemia^[109].

Statins exhibit pleiotropic effects and dose-dependent alterations in hepatic enzymes^[136]. Kruppel-like factor 2 (KLF-2), a component of hepatic endothelium, is induced in early stages of LC, serving as a defense mechanism against fibrosis and endothelial dysfunction during disease progression, albeit insufficiently. Statins enhance KLF-2 expression through the Rac1-MEK5-ERK5-MEF2 pathway, augmenting their protective effects. Atorvastatin, simvastatin, rosuvastatin, fluvastatin, and lovastatin have demonstrated benefits in reducing the risk of hepatic decompensation, variceal bleeding, and mortality, especially in compensated cirrhotic patients^[136,137]. Statin use is associated with a lower risk of LC progression in chronic hepatitis B patients^[138]. Nationwide studies revealed statin use's correlation with reduced HCC development, regardless of DM or LC presence^[139]. Statin therapy is notably advantageous for males, individuals with DM, and those with high fibrosis-4 index at study initiation^[140]. In patients with DM, statin use is linked to a reduced likelihood of advanced fibrosis^[141].

The management of obesity in liver disease patients is complex due to potential exacerbation of sarcopenia. Therefore, it is recommended to implement moderate caloric restriction (reducing by 500-800 kcal/d) while ensuring a standard or higher protein intake to prevent muscle catabolism, aiming to achieve a weight reduction of 5%-10%. The use of anti-obesity medications is not recommended in these patients, and the evidence for bariatric procedures is insufficient to make recommendations^[28].

Regarding the potential remission of DM, liver transplantation is less effective in patients with impaired beta cell function. This raises the need for a reevaluation of the indication and timing of this procedure in these patients^[17].

Hypoglycemia

The primary objective in treating hypoglycemia is the swift correction of blood glucose levels to a safe range, minimizing the risk of cerebral damage and alleviating symptoms. In conscious individuals, the recommended approach involves oral administration of 15-20 g of glucose, although any carbohydrate containing glucose can be utilized. Glucose levels should be re-evaluated after 15 min, and if hypoglycemia persists, the treatment should be repeated. Following the increase in blood glucose, a meal should be consumed to prevent recurrence of hypoglycemia. Glucagon is reserved for severe hypoglycemia and is administered parenterally (intramuscular, intravenous, or subcutaneous)^[56,142,143]. In most cases, managing hypoglycemia involves an increased caloric intake throughout the day. Additionally, individuals are advised to abstain from alcohol and consider altering or adjusting doses of hypoglycemic drugs such as insulin and sulfonylureas^[144].

Managing DM in cirrhotic patients can be complicated by cognitive impairment due to hepatic encephalopathy, affecting their ability to avoid dosing errors, miss meals, and recognize hypoglycemic episodes^[28]. Consequently, many patients will require greater support from their social network. The effective management of hypoglycemia in patients with DM and LC necessitates prevention of further episodes. Therefore, patients using oral antidiabetic agents require dose adjustments or changes in the prescribed medication. Similarly, insulin users may need dosage reductions or, in some cases, temporary discontinuation^[59].

Sarcopenia

The management of sarcopenia necessitates a multidimensional approach emphasizing lifestyle modifications, nutrition, exercise, and adjuvant pharmacotherapy. Recommendations include discontinuation of alcohol and tobacco use, optimizing sleep quality, and enhancing psychological well-being. ¹⁵ The European Association for the Study of the Liver (EASL) and the European Society for Clinical Nutrition and

9
Metabolism (ESPEN) advocate for a daily caloric intake of 35-40 kcal/kg and a protein intake of 1.2-1.5 g/kg^[145,146]. Additionally, considering the potential benefits of BCAA supplementation, EASL recommends its long-term use at a dosage of 0.25 g/kg/d for patients with advanced hepatic dysfunction and a history of hepatic encephalopathy^[146]. ESPEN suggests reducing fasting periods, having meals at intervals of 2-3 h, and incorporating a pre-sleep snack comprising 50 g of carbohydrates and 20 g of protein^[145].

Moderate-intensity aerobic and resistance exercises enhance cardiovascular capacity and muscle mass, significantly improving the quality of life, especially in patients with compensated LC and to a lesser extent in decompensated LC patients^[21]. Treatments targeting ammonia reduction, hormonal supplements, and myostatin inhibitors are still under investigation^[21,22,147].

Hypogonadotropic hypogonadism

Addressing sexual dysfunction in cirrhotic patients requires a multidisciplinary approach. In males with LC and low testosterone levels, supplementation has shown additional benefits in total body lean mass and bone mass. Therefore, it could be considered as complementary therapy to enhance frailty in cirrhosis^[148]. Regarding the use of phosphodiesterase-5 inhibitors (PDE-5i), four are approved by the Food and Drug Administration: Sildenafil, tadalafil, 3 avanafil, and vardenafil. None of these are recommended for Child-Pugh C patients, and if prescribed, dosage reduction is common due to decreased clearance^[24]. Currently, the use of PDE-5i is being evaluated for potential benefits in portal hemodynamics and hepatic encephalopathy^[149].

In women, treatment should address reproductive and/or sexual dysfunction. Fundamental intervention strategies include lifestyle modifications and psychological support^[24]. Transdermal testosterone supplementation has been assessed for short-term efficacy in improving female sexual dysfunction, with few significant androgenic adverse effects. However, there are no studies on its use in cirrhotic patients^[150]. Regarding reproductive dysfunction, women with compensated LC and minimal portal

hypertension typically maintain regular menstrual cycles and preserved fertility. If pregnancy is undesirable, contraception should be offered^[151]. In women with compensated LC, there are no restrictions on the use of any hormonal contraceptive methods, whereas in those with severe and decompensated LC, risks often outweigh the benefits^[152].

Liver transplantation restores physiological levels of testosterone, estradiol, SHBG, gonadotropins, and PRL^[45].

Thyroid dysfunction

Hypothyroidism: Patients with LC and hypothyroidism must be treated immediately according to current guidelines. LC can cause malabsorption, so severely **hypothyroid patients with cirrhosis may require higher doses of levothyroxine**^[67,153]. If the alterations are consistent with subclinical hypothyroidism, other factors such as TSH level, presence of autoantibodies, and patient's age will be evaluated. Current guidelines for subclinical hypothyroidism do not emphasize the hepatic function status in the treatment decision algorithm^[72].

Euthyroid sick syndrome: Isolated low FT3 levels are not recommended to be treated, despite the numerous available studies; the efficacy of hormonal therapy in cases of euthyroid sick syndrome remains unclear^[72].

Hyperthyroidism: Like hypothyroidism, immediate treatment should be initiated in cases of overt hyperthyroidism, following current guidelines. Considering the known effect of thiamazole on liver function, there are no controlled studies in Child-Pugh B or C patients. Therefore, it is recommended to start with a dose of 20 mg in Child-Pugh A patients, followed by continuous monitoring of liver function^[154-156]. Seventy-seven to eighty-three percent of hyperthyroid patients who initiate treatment early achieve normalization of liver enzymes^[157]; however, approximately 1%-2% of patients develop fulminant hepatitis^[35]. Propylthiouracil has a higher risk of liver failure and is not

considered an ideal therapeutic option for managing hyperthyroidism in patients with LC. Definitive treatments such as radioactive iodine therapy or thyroidectomy can be considered based on the patient's clinical condition^[67]. There is no evidence to suggest that liver transplantation restores thyroid function^[45].

Hepatic bone disease

The recommendations for osteoporosis treatment in cirrhotic patients do not differ from general guidelines. Lifestyle changes, cessation of tobacco and alcohol use, corticosteroid dose reduction, and increasing physical activity as much as possible to improve spinal mechanics and strength are recommended^[77]. Caloric intake recommendations vary between 30-50 kcal/kg/d, with protein intake of 1.0-1.8 g/kg/d, depending on the severity of malnutrition^[158]. While treatment is provided to patients with osteoporosis due to the high risk of fractures, given that osteopenia is a risk factor for vertebral fractures, prophylactic treatment is recommended in patients with osteopenia^[159].

Regarding supplements, the total calcium intake should be 1000-1500 mg/d, with calcium carbonate being the most consumed supplement. It is recommended to take it with meals^[77,158,160]. In patients with LC and proven vitamin D deficiency, efforts should be made to restore vitamin D levels^[38]. Although vitamin D deficiency has been linked to higher overall mortality and hepatic decompensation in patients with advanced CLD, there is insufficient evidence to routinely recommend vitamin D supplementation in patients with LC^[38,161,162].

Hormonal therapy should be individualized and could be applied in patients with hypogonadism; however, estrogens may increase the risk of cholestasis^[77,79].

Regarding treatments that enhance bone formation, intermittent parathyroid hormone administration lacks sufficient evidence in patients with advanced liver disease. For drugs reducing bone resorption, oral bisphosphonates may cause esophagitis or esophageal ulcers; hence, the parenteral use of bisphosphonates such as zoledronic acid is recommended. Due to its annual administration, compliance can be

improved^[158]. Etidronate and alendronate have been used in patients with primary biliary cirrhosis, and after 1-2 years of treatment, there was improvement in BMD with few adverse effects^[160].

Raloxifene has been used as a therapeutic option for osteoporosis, but it has not yet been applied in cirrhotic patients. However, it might have a potential beneficial effect on lumbar spine BMD^[77,158].

Adrenal insufficiency

Unlike diagnosis, there is no controversy in the treatment of critically ill patients. Intravenous hydrocortisone at a dose of 200 mg/d to 300 mg/d divided into 3 to 4 doses is indicated, with subsequent progressive titration based on the patient's clinical evolution. For non-critically ill patients without symptoms, literature is limited; therefore, oral hydrocortisone at a dose of 15 mg to 20 mg divided into two doses per day is suggested, only in cases of persistent hypotension and hyponatremia^[86,87,91,163,164].

Growth hormone dysfunction

In all scenarios, the evidence from research demonstrating a clear benefit for patients replacing GH leans towards its use for periods ranging from 6 months to 12 months. Even in studies with a limited number of patients, the primary benefit observed is the prevention of muscle mass loss. In cases where a deficiency of GH is demonstrated, especially if the patient is a candidate for liver transplantation, replacement therapy is administered *via* daily injections, independent of body weight and based on age (age below 30 years: 0.4-0.5 mg/d; 30 to 60 years: 0.2-0.3 mg/d; and age over 60 years: 0.1-0.2 mg/d), with subsequent dose titration to maintain IGF-1 within the standard deviation of -2 to 2, always assessing the clinical benefit and side effects. There is no data in LC with long-acting GH preparations. For individuals in whom a decrease in GH is not demonstrated, there is no evidence to adequately justify its use currently. Any apparent beneficial effects do not persist over time, and potential side effects, such as alterations in glucose metabolism and possible neoplasms, have a latency period^[92,94,95,165-168].

Although liver transplantation restores physiological levels of GH, IGF-1, and IGFBP-3^[45], it achieves only partial restoration of growth, resulting in pubertal delay and reduced adult height^[1].

Secondary hyperaldosteronism

The treatment of LC as an underlying condition is a crucial part of managing secondary hyperaldosteronism. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are the first-line antihypertensive agents due to their nephroprotective benefits, and dietary sodium restriction is recommended^[47,48].

Managing ascites involves enhancing renal sodium excretion with diuretics and restricting sodium intake. Large-volume paracentesis and transjugular intrahepatic portosystemic shunts are also useful in managing refractory ascites. For cirrhotic patients with refractory ascites, the first-line standard of care is the mineralocorticoid antagonist, spironolactone. However, the natriuretic doses of aldosterone antagonists have not been studied in patients with heart failure^[46]. Although loop diuretics have much higher natriuretic potency than distal diuretics, high-dose furosemide (up to 160 mg/d) in cirrhotic patients without renal failure produces satisfactory natriuresis in only 50% of patients. In cases of marked hyperaldosteronism, there is no response to furosemide, necessitating the use of high doses of spironolactone (400 to 600 mg/d). Thus, the International Club of Ascites defined diuretic resistance in patients with ascites as the lack of response to a low-sodium diet and treatment with high-dose diuretics (400 mg/d of spironolactone and 160 mg/d of furosemide)^[46]. Adverse effects of spironolactone, given its partial affinity for progesterone and androgen receptors, include painful gynecomastia and hypogonadism in males^[169]. On the other hand, it may have beneficial effects in polycystic ovary syndrome^[170].

Eplerenone is a more selective mineralocorticoid receptor antagonist with greater specificity for the mineralocorticoid receptor, resulting in fewer side effects related to gynecomastia and hypogonadism compared to spironolactone^[171].

Finerenone is a nonsteroidal mineralocorticoid receptor antagonist with high potency and strong selectivity for the mineralocorticoid receptor, overcoming significant barriers seen in previous generations of mineralocorticoid receptor antagonists^[171]. Additionally, finerenone prevents aldosterone-induced endothelial cell apoptosis and smooth muscle cell proliferation, thereby reducing vascular remodeling^[172].

CONCLUSION

LC exerts a significant impact on the endocrine system, although it may go unnoticed despite being associated with increased morbidity and mortality. For this reason, a comprehensive and multidisciplinary approach is necessary, allowing not only the management of hepatic pathology but also timely diagnosis and treatment of associated endocrinological disorders.

ARTICLE HIGHLIGHTS

Research background

Hepatic pathophysiology and the endocrine system are intricately connected, and there is endocrine dysfunction in liver cirrhosis (LC). The liver synthesizes hormones and impacts endocrine function in chronic liver diseases. We address the endocrine pathologies in cirrhotic patients, offering an updated narrative on epidemiology, pathophysiology, diagnosis, and treatment.

Research motivation

To shed light on the critical yet frequently neglected aspect of endocrinopathies in cirrhotic patients. Despite the profound prognostic implications, the evaluation of endocrine pathologies in individuals with cirrhosis is commonly overlooked by specialists. Our comprehensive analysis seeks to address this gap in understanding by providing a meticulous exploration of the epidemiology, pathophysiology, diagnosis, and treatment of endocrine disturbances in cirrhotic patients.

Research objectives

To comprehensively explore the epidemiology, pathophysiology, diagnosis, and treatment of endocrine disturbances in patients with LC. Our focus encompasses a spectrum of endocrine disorders, including diabetes mellitus (DM), hypoglycemia, sarcopenia, hypogonadotropic hypogonadism, thyroid dysfunction, hepatic bone disease, adrenal insufficiency, growth hormone dysfunction, and secondary hyperaldosteronism.

Research methods

A comprehensive narrative review was conducted by searching PubMed/Medline, EMBASE, and Scielo databases using specific keywords related to hepatocrinology, LC, and various endocrine disturbances. The search included a wide range of study types, such as systematic reviews, meta-analyses, clinical trials, retrospective and prospective studies, case reports, and narrative reviews.

Research results

In LC, the most common endocrine disturbance involves insulin resistance, DM, and hypoglycemia. Accurate diagnosis of these issues, along with the other associated endocrinopathies, requires comprehensive biochemical and hormonal tests. Timely identification and treatment of these endocrine imbalances have a substantial impact on reducing morbidity and mortality, emphasizing the importance of early intervention for improved patient outcomes.

Research conclusions

This study introduces novel perspectives in recognizing the often-overlooked impact of LC on the endocrine system, emphasizing the need for a comprehensive and multidisciplinary approach. While not proposing new theories, it sheds light on the critical importance of timely diagnosis and treatment of associated endocrinological disorders, aiming to enhance patient care and outcomes.

Research perspectives

Future research in cirrhosis and endocrinopathies should focus on uncovering precise mechanisms through which cirrhosis influences the endocrine system, providing insights into associated disorders. Evaluating emerging treatment modalities and their impact on hepatic and endocrine outcomes, especially in sarcopenia, where investigations involve ammonia reduction, hormonal supplements, and myostatin inhibitors, is crucial. Tirzepatide and retatrutide show promise in improving hepatic liver disease, but their specific effects on managing DM in cirrhotic individuals need further elucidation.

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Figure Legends

Figure 1 Pathophysiology of liver cirrhosis and associated endocrinopathies. A: Pathophysiology of liver cirrhosis (LC); B: Pathophysiology of the endocrinopathies associated to LC. AD: Antidiabetic drug; AVP: Arginine vasopressin; BCAA: Branched-chain amino acid; BP: Blood pressure; GH: Growth hormone; IGF-1: Insulin-like growth factor 1; IGFBP: Insulin-like growth factor binding protein; RAAS: Renin-angiotensin-aldosterone system; SHBG: Sex hormone-binding globulin; SNS: Sympathetic nervous system; T3: Triiodothyronine; T4: Thyroxine.

Figure 2 Summary of diagnostic tests used in the approach to endocrinopathies associated with liver cirrhosis. The asterisk (*) represents that adrenal insufficiency

should be evaluated if there is refractory hypotension, sodium less than 125 mmol/L, and high-density lipoproteins less than 0.39 mmol/L. BMD: Bone mineral density; BMI: Body mass index; CGM: Continuous glucose monitoring; CT: Computed tomography; DXA: Dual-energy X-ray absorptiometry; FIB-4 index: Fibrosis-4 index; FSFI: Female Sexual Function Index; FSH: Follicle-stimulating hormone; FT: Free testosterone; GH: Growth hormone; HbA1c: Hemoglobin A1c; IGF-1: Insulin-like growth factor 1; IIEF: International Index of Erectile Function; IV: Intravenous; L3: 3rd lumbar vertebrae; LH: Luteinizing hormone; LLN: Lower limit of normality; MRI: Magnetic resonance imaging; OGGT: Oral glucose tolerance test; PA: Primary aldosteronism; PAC: Plasma aldosterone concentration; POI: Primary ovarian insufficiency; PRA: Plasma renin activity; PRC: Plasma renin concentration; PRL: Prolactin; SHBG: Sex hormone-binding globulin; TSH: Thyroid-stimulating hormone; TT: Total testosterone.

Table 1 Summary of pharmacological interventions in endocrinopathies associated with liver cirrhosis

Endocrinopathy	Interventions	Comments	Ref.
Diabetes mellitus	Therapeutic goals: Compensated cirrhosis: FPG 4.44-7.22 mmol/L, PP glucose < 9.99 mmol/L; [28,50] decompensated cirrhosis: FPG 5.00-8.32 mmol/L, PP glucose < 11.10 mmol/L, and pre-meal glucose 5.55-11.10 mmol/L		
	Metformin	Maximum 1500 mg/d. Do not use in hypoxemia, dehydration, sepsis, or Child-Pugh B and C	[50,109]
	Sulfonylureas	Can be used in low doses in Child-Pugh A. Contraindicated in Child-Pugh B and C	[28,50,100,109]
	Meglitinides	Do not use repaglinide. Nateglinide can be used in Child-Pugh A and B in lower doses	[28,50]
	Thiazolidinediones	Do not use rosiglitazone. Pioglitazone can be used in Child-Pugh A	[28,50,109]
	DPP-4 inhibitors	Can be used in Child-Pugh A without modifying the dose, except for vildagliptin. Use with caution in Child-Pugh B, but not in Child-Pugh C	[50,109]
	GLP-1 RA	Can be used in Child-Pugh A without modifying the dose. Use with caution in Child-Pugh B, but not in Child-Pugh C, due to limited data	[50,109]
	Unknown for Tirzepatide and Retatrutide		
	SGLT-2i	Can be used in Child-Pugh A, starting with lower doses. Use with caution in Child-Pugh B but avoid in Child-Pugh C due to the risk of dehydration and hypotension	[28,109]

Alpha-glucosidase inhibitors	Can be used in Child-Pugh A and B but are not recommended in Child-Pugh C [50,109]
Insulin	Reserve for those unable to use oral medications, fail to achieve adequate glycemic control, or in cases of sepsis, encephalopathy, bleeding, or acute kidney injury. It is the choice in DM and decompensated LC; start with 0.1-0.2 IU/kg/d (higher if blood glucose is very high). Adjust the dose based on blood glucose, varying by 2 units every 3 d if necessary. Add rapid-acting insulin if goals are not achieved, starting with 4 units or 10% of basal insulin and increasing by 1-2 units every 3-4 d as needed. Prefer analog insulins for a lower risk of hypoglycemia [28,109]
Statins	Generally recommended for males, individuals with diabetes, and those with a high Fibrosis-4 index at the beginning of the study [140]
Liver transplantation	The worse the beta cell function, the less effective liver transplantation will be in achieving DM remission [17]
Hypoglycemia	New episodes should be prevented by adjusting the dose or modifying the drugs used [56,142,143]
	15-20 g of oral glucose For conscious patients. Reassess in 15 min and repeat if necessary [56,142,143]
	Parenteral glucagon For unconscious patients or those with severe hypoglycemia [56,142,143]
Sarcopenia	Nutritional support Caloric intake of 35-40 kcal/kg and protein intake of 1.2-1.5 g/kg. Eat at intervals of 2-3 h and include a bedtime snack with 50 g of carbohydrates and 20 g of protein [145,146]

	BCAA	Long-term supplementation at a dose of 0.25 g/kg/d	[146]
	Exercise	Recommended moderate-intensity aerobic and resistance exercises	[21]
	Others	Treatments to reduce ammonia, hormonal supplements, and myostatin inhibitors are still under study	[21,22,147]
Male hypogonadism	Testosterone supplementation	Considered adjunctive therapy to improve frailty	[148]
	PDE-5i	Sildenafil, tadalafil, avanafil, and vardenafil are FDA-approved and can be used in Child-Pugh A and B at lower doses	[24]
	Liver transplantation	Restores physiological levels of testosterone, estradiol, SHBG, gonadotropins, and prolactin	[45]
Female hypogonadism	Lifestyle modifications and psychological support	should be included	[24]
	Contraception	In compensated cirrhosis, hormonal contraceptives can be used without restriction, but in decompensated cirrhosis, the risks outweigh the benefits	[152]
	Liver transplantation	Restores physiological levels of testosterone, estradiol, SHBG, gonadotropins, and prolactin	[45]
Overt hypothyroidism	Levothyroxine	Immediate treatment per general recommendations, considering higher doses might be necessary due to malabsorption	[67,153]
	Subclinical hypothyroidism	Treatment per general recommendations. Liver function is not part of the treatment decision	[72]
	Euthyroid	Hormonal treatment is not recommended	[72]

syndrome			
Hyperthyroidism	Thiamazole	Recommended starting dose of 20mg in Child-Pugh A with continuous monitoring of liver function. Not recommended in Child-Pugh B and C	[154-156]
	Propylthiouracil	Its use is not recommended	[67]
	Definitive treatments	Radioactive iodine therapy or thyroidectomy based on patient's need and clinical condition	[67]
	Liver transplantation	Not recommended to restore thyroid function	[45]
Hepatic bone disease	Calcium	1000-1500 mg/d, taken with food	[77,158,160]
	25-OH vitamin D	Supplement only if there is a deficiency of vitamin D	[38]
	PTH	There is not enough evidence in advanced cirrhosis	[158]
	Bisphosphonates	Parenteral use is recommended	[158]
	Raloxifene	There is not enough evidence in cirrhosis	[77,158]
Adrenal insufficiency	Hydrocortisone	Critically ill patients: 200-300 mg/d intravenously, divided into 3 to 4 doses, with progressive titration based on the patient's clinical evolution; non-critically ill patients without symptoms: 15-20 mg/d orally, divided into 2 doses, only if persistent hypotension and hyponatremia are present	[86,87,91,163,164]
Growth hormone dysfunction	GH	If GH deficiency is demonstrated: 0.4-0.5 mg/d (< 30 years), 0.2-0.3 mg/d (30-60 years), 0.1-0.2 mg/d (> 60 years), with dose titration to maintain IGF-1 within the standard deviation of -2 to 2.	[92,94,95,165-168]
Secondary	Loop diuretics	High doses of furosemide (up to 160 mg/d) in cases without renal	[46]

hyperaldosteronism

insufficiency, although with limited effectiveness

Mineralocorticoid

Spirolactone (up to 400-600 mg/d). Eplerenone is more selective with [46,171]

receptor antagonists

fewer side effects. Finerenone is a potent and selective non-steroidal

antagonist

BCAA: Branched chain amino acid; DM: Diabetes mellitus; FDA: Food and Drug Administration; FPG: Fasting plasma glucose; GH: Growth hormone; GLP-1 RA: Glucagon-like peptid 1 receptor agonist; IGF-1: Insulin-like growth factor 1; LC: Liver cirrhosis; PDE-5i: Phosphodiesterase 5 inhibitor; PP: Posprandial; SGLT-2i: Sodium-glucose cotransporter 2 inhibitor; SHBG: Sex hormone-binding globulin.

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