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Interplay Between the Pituitary-Adrenal Axis and Thyroid Hormones in Acute-on-Chronic Liver Failure: Mechanisms, Prognostic, and Therapeutic Implications [Review]

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ABSTRACT
Acute-on-chronic liver failure (ACLF) is a critical syndrome marked by the rapid deterioration of liver function in patients with underlying chronic liver disease, often leading to multi-organ failure and high short-term mortality. This review illustrates the interactions between the hypothalamic-pituitary-adrenal (HPA) axis and thyroid hormone metabolism in ACLF. Endocrine disruptions, including adrenal insufficiency and non-thyroidal illness syndrome (NTIS), are common and associated with increased disease severity and poorer outcomes. These hormonal imbalances contribute to systemic inflammation and organ dysfunction, highlighting their potential as prognostic markers and therapeutic targets. The review discusses the prevalence, diagnostic challenges, and treatment outcomes of adrenal and thyroid dysfunctions in ACLF and considers the inclusion of endocrine failure in ACLF diagnostic criteria. Future research should focus on elucidating the mechanisms of endocrine dysregulation and validating effective hormonal therapies in ACLF.

Keywords: ACLF, HPA, NTIS, liver, dysfunction

INTRODUCTION

ACLF represents a critical juncture in hepatology, characterized by the sudden exacerbation of liver dysfunction in individuals with pre-existing chronic liver disease. This syndrome is distinguished by rapid hepatic decompensation, often precipitated by identifiable triggers, leading to multi-organ failure and a high short-term mortality rate. The pathophysiology of ACLF is complex, involving a confluence of systemic inflammation, immune dysregulation, and metabolic disturbances. Among the myriad systems affected, the endocrine interplay, particularly between the hypothalamic-pituitary-adrenal (HPA) axis and thyroid hormones, has garnered significant attention due to its profound implications on disease progression and patient outcomes.**[1]**.

The HPA axis serves as a central regulator of the body's response to stress, orchestrating the release of glucocorticoids, primarily cortisol, which modulate various physiological processes, including metabolism, immune response, and vascular tone**[2]**. In the setting of ACLF, evidence suggests a disruption of this axis, leading to adrenal insufficiency. Clinical observations have indicated that patients with cholestatic liver disorders exhibit significant alterations in HPA axis function, manifesting as impaired cortisol synthesis and secretion. This dysfunction may exacerbate the systemic inflammatory milieu characteristic of ACLF, thereby contributing to the progression of organ failures**[3]**.

Concurrently, thyroid hormone metabolism undergoes notable changes in ACLF. The liver plays a pivotal role in the conversion of thyroxine (T4) to the more active triiodothyronine (T3) via deiodination processes. In ACLF, this conversion is often impaired, leading to a state referred to as non-thyroidal illness syndrome (NTIS), characterized by low serum T3 levels with normal or low T4 and thyroid-stimulating hormone (TSH) concentrations. Studies have demonstrated that patients with ACLF exhibit altered thyroid hormone profiles, which correlate with disease severity. Specifically, reduced free T3 (fT3) levels have been associated with increased risks of hepatic decompensation, progression to ACLF, and liver-related mortality **[4].**

The intricate relationship between the HPA axis and thyroid hormones in ACLF underscores the importance of a comprehensive approach to patient management. By exploring the mechanisms driving endocrine dysfunction and recognizing their prognostic implications, clinicians can better stratify risk and tailor therapies to address the multifaceted challenges presented by this syndrome. Future research should focus on delineating the precise

pathways of endocrine disruption in ACLF and evaluating the therapeutic potential of interventions targeting these pathways.

Understanding Acute-on-Chronic Liver Failure and Related Organ Dysfunction.

ACLF is defined by the acute decompensation of chronic liver disease, leading to liver failure and the failure of one or more extrahepatic organ systems. This syndrome is distinct from mere decompensated cirrhosis due to its rapid progression and high mortality rate. The prevalence of ACLF varies globally, influenced by regional etiological factors and healthcare practices. In Western countries, alcohol-related cirrhosis is the most common cause of chronic liver disease, with bacterial infections being the most important precipitant of ACLF **[5]**.

The liver's impaired detoxification capacity results in toxin accumulation, exacerbating organ dysfunction. Renal impairment, often manifesting as hepatorenal syndrome, is common in ACLF and involves complex interactions between liver and kidney dysfunctions, including alterations in renal blood flow and systemic inflammation**[6]**. Neurologically, hepatic encephalopathy ranges from mild cognitive impairment to deep coma, primarily due to the accumulation of neurotoxins like ammonia. Systemic inflammation and cytokine release can lead to cardiovascular instability, with patients exhibiting features of cirrhotic cardiomyopathy, such as impaired cardiac contractility**[7]**. Pulmonary complications, including acute respiratory distress syndrome (ARDS) and hepatic hydrothorax, further complicate clinical management and worsen prognosis**[8]**. Additionally, hepatic dysfunction leads to significant coagulopathies, increasing the risk of both bleeding and thrombotic events **[9]**.

In addition to the aforementioned organ dysfunctions, endocrine abnormalities, particularly involving the adrenal and thyroid glands, are increasingly recognized in ACLF. The liver plays a pivotal role in hormone metabolism and regulation; thus, hepatic dysfunction can significantly impact endocrine homeostasis. Stress-induced alterations in the hypothalamic-pituitary-adrenal (HPA) axis are common in ACLF. Systemic inflammation and sepsis, frequent in ACLF, can impair adrenal function, leading to adrenal insufficiency. This condition is characterized by inadequate cortisol production relative to the body's increased demands during stress, potentially exacerbating hemodynamic instability and increasing susceptibility to infections **[10].**Thyroid hormone metabolism is also notably affected in ACLF. Patients often exhibit a state known as non-thyroidal illness syndrome (NTIS), characterized by low serum levels of triiodothyronine (T3) and normal or low thyroxine (T4) without a compensatory increase in thyroid-stimulating hormone (TSH). This alteration is believed to result from impaired peripheral conversion of T4 to T3, influenced by systemic inflammation and hepatic dysfunction. The presence of NTIS in ACLF has been associated with worse clinical outcomes, including higher mortality rates **[11]**.

Assessment of the Pituitary-Adrenal Axis in ACLF Patients

In the context of ACLF, pituitary-adrenal axis dysfunction, often referred to as adrenal insufficiency (AI), is characterized by an inadequate production or response of cortisol relative to the body's increased demands during critical illness. This condition is commonly observed in patients with cirrhosis and ACLF, where the hypothalamic-pituitary-adrenal (HPA) axis may be impaired due to systemic inflammation and hepatic dysfunction. The pathophysiology involves a deficient adrenal response to stress, leading to insufficient cortisol levels to meet physiological needs **[12]**.

Diagnosing adrenal insufficiency in ACLF is challenging due to the altered cortisol-binding dynamics in liver disease. Traditional diagnostic tests, such as the standard-dose (250 µg) adrenocorticotropic hormone (ACTH) stimulation test, are commonly used to assess adrenal function. However, their interpretation requires caution, as cirrhosis can affect cortisol metabolism and binding proteins, potentially leading to misleading results. Some studies suggest that measuring free cortisol levels or using low-dose (1 µg) ACTH stimulation tests may provide more accurate assessments in this population **[10]**.

Prevalence of Adrenal Insuffeciency.

The prevalence of AI in this patient population varies across studies, influenced by differences in diagnostic criteria and assessment methods. **Marik et al., (2005),**conducted a study involving 340 critically ill cirrhotic patients, utilizing the low-dose short synacthen test (LDSST) to assess adrenal function. They reported an overall AI prevalence of 72%, with 33% in patients presenting with acute liver failure and 66% in those with chronic liver failure. Notably, 62% of short-term liver transplant recipients and 92% of long-term recipients exhibited AI. High-density lipoprotein (HDL) levels were identified as a predictive factor for AI prevalence**[13]**.

In a prospective study by**Thevenot et al., (2011)**, 30 septic cirrhotic patients were evaluated using serum total cortisol measurements 60 minutes after a standard short synacthen test (SST), with a threshold of 510.4 nmol/L to define AI. The study found an AI prevalence of 10%. Additionally, salivary cortisol levels were assessed and found to correlate significantly with serum free cortisol ($P < 0.0001$), suggesting that salivary cortisol could serve as a suitable marker for adrenal function evaluation in cirrhotic patients when serum-free cortisol measurements are unavailable**[14]**.

In another prospective observational study in the United Kingdom, researchers assessed the adrenal function in 56 patients with acute liver failure (ALF) and 36 with acute-on-chronic liver failure (ACLF) using the SST. They reported AI in 58% of ACLF patients and 48% of ALF patients. The study also found that lower HDL levels were associated with AI and worse outcomes in both patient groups**[15].**

Du Cheyron et al., (2008)examined 50 critically ill cirrhotic patients and identified AI in 62% of cases, using baseline cortisol levels below 414 nmol/L or a delta cortisol (the difference between baseline and post-stimulation levels) below 250 nmol/L as diagnostic criteria. Similarly, studies focusing on cirrhotic patients with sepsis reported AI prevalence rates of 77% and 68%, respectively, when applying comparable diagnostic thresholds**[16]**.

In a study of 137 outpatients with advanced chronic liver disease, median adrenocorticotropic hormone (ACTH) levels decreased from 44.0 pg/ml in subclinical portal hypertension to 20.0 pg/ml in patients with further decompensation ($p = 0.006$). Similarly, median serum total cortisol levels declined from 13.9 μg/dl in the subclinical stage to 9.2 μg/dl in further decompensation ($p = 0.091$). Lower total cortisol levels were independently associated with increased risks of bacterial infections, further decompensation, acute-on-chronic liver failure, and liver-related death **[17]**.

ACLF is often precipitated by acute insults such as infections, alcohol consumption, or viral hepatitis reactivation, superimposed on chronic liver disease. These triggers can lead to an exaggerated systemic inflammatory response, contributing to hepatic and extra-hepatic organ failure**[18]**. Corticosteroids, by modulating the immune response and reducing inflammation, have been proposed as a therapeutic option to mitigate this hyperinflammatory state. However, their efficacy and safety in ACLF are subjects of ongoing debate.

A prospective multicenter clinical trial involving 171 patients with HBV-related ACLF evaluated the efficacy of a 7-day methylprednisolone regimen. The study reported an increase in the 6-month survival rate among patients receiving steroid therapy, suggesting potential benefits in this subgroup**[19]**.In contrast, a retrospective study conducted over a decade in East China assessed steroid treatment in patients with HBV-related ACLF. The findings indicated that steroid therapy did not improve transplant-free survival rates, casting doubt on its effectiveness in this context**[20]**.

Autoimmune hepatitis (AIH) can present acutely and progress to ACLF.Corticosteroids are the mainstay of treatment in AIH due to their immunosuppressive effects.A review in the Journal of Hepatology highlighted that flares of AIH can precipitate ACLF, and in such cases, corticosteroid therapy has been effective, leading to clinical improvement**[21]**.However, the efficacy of steroids in AIH-related ACLF may be influenced by the timing of initiation and the extent of liver damage. Early recognition and prompt treatment are crucial to prevent irreversible liver injury and improve outcomes.

A retrospective analysis of patients with acute liver failure (ALF) and subacute liver failure (SALF) found that corticosteroid treatment improved spontaneous survival rates, particularly in patients with lower Model for End-Stage Liver Disease (MELD) scores and less severe hepatic encephalopathy. The study emphasized the importance of early intervention, noting that patients who received steroids within two weeks of symptom onset had better outcomes**[22]**.

The role of corticosteroid therapy in ACLF is complex and varies depending on the underlying etiology, disease severity, and timing of administration. While evidence supports the use of steroids in specific contexts, such as AIH-related ACLF and certain cases of HBV-related or alcohol-associated ACLF, their application must be individualized.

Thyroid Dysfunction in ACLF

Thyroxine (T4) and triiodothyronine (T3) are pivotal thyroid hormones that regulate metabolism, growth, and development. Their production and release are tightly governed by the hypothalamic–pituitary–thyroid (HPT) axis. Specifically, the hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the pituitary gland to release thyroid-stimulating hormone (TSH). TSH then prompts the thyroid gland to secrete T4 and T3. In the liver, T4 is largely converted into the more bioactive T3 by deiodinase enzymes. The liver also synthesizes thyroid-binding globulin (TBG), a key carrier of thyroid hormones in circulation, underscoring the crucial role of hepatic function in preserving thyroid hormone homeostasis**[23]**.

Thyroid dysfunction is frequently noted in patients with acute-on-chronic liver failure (ACLF) and has significant clinical relevance. A large-scale study involving 437 individuals with cirrhosis revealed that 39.3% of those who experienced acute decompensation had non-thyroidal illness syndrome (NTIS). Among patients who progressed to ACLF, this prevalence rose to 72.1%, indicating a close relationship between increasing disease severity and thyroid dysfunction **[11]**.

In a separate cohort of 100 patients with decompensated cirrhosis, low free triiodothyronine (FT3) levels were detected in 41%. This proportion increased to 50% among those with hepatic encephalopathy (HE) and was observed in 32% of non-survivors. Furthermore, hypothyroidism (evidenced by elevated TSH) was present in 20% of all participants, 26.3% of those with HE, and notably in 50% of non-survivors **[24]**.

Additional research shows that diminished free T3 (fT3) levels in advanced chronic liver disease (ACLD) correlate with a greater likelihood of decompensation, ACLF, and mortality related to liver disease, emphasizing the prognostic significance of thyroid hormone markers**[4]**.Moreover, a recent investigation of 119 patients demonstrated that a reduced fT3/fT4 ratio was linked to more severe liver disease and elevated mortality. These findings suggest that thyroid hormone profiling could prove valuable in managing and predicting outcomes in ACLF**[25]**.

The interplay between thyroid hormones and liver function is complex. Thyroid hormones regulate various hepatic functions, including lipid metabolism, bile acid synthesis, and detoxification processes. Conversely, liver impairment can alter thyroid hormone metabolism, leading to systemic effects. A review in Hepatology highlighted that thyroid hormone signaling is intricately linked with hepatic activity, and disruptions in this relationship can exacerbate liver disease progression**[26]**.

Given the association between thyroid dysfunction and poor outcomes in ACLF, there is interest in exploring thyroid hormone supplementation as a potential therapeutic strategy. However, clinical evidence supporting this approach is limited, and further research is necessary to determine its efficacy and safety. Currently, management focuses on monitoring thyroid function and addressing underlying liver disease.

Shall We Include Endocrinal Failure In ACLF Definition?

The European Association for the Study of the Liver–Chronic Liver Failure (EASL-CLIF) Consortium defines ACLF by the failure of six organ systems: liver, kidney, brain, coagulation, circulation, and respiration **[27]**.

Endocrine disturbances, particularly in thyroid hormone levels, are frequently observed in individuals with liver disease. Non-thyroidal illness syndrome (NTIS), marked by decreased triiodothyronine (T3) and thyroxine (T4) levels alongside normal or low thyroid-stimulating hormone (TSH), has been detected in patients undergoing acute decompensation of cirrhosis and ACLF. Recent investigations have examined the progression of NTIS in this group, suggesting a possible link between endocrine dysregulation and ACLF **[11]**. In addition, adrenal insufficiency (AI), also referred to as adrenal failure, constitutes a recognized complication in cirrhosis and ACLF. Frequently termed “hepato-adrenal syndrome” in these cases, AI arises when cortisol production fails to meet the heightened physiological demands of critical illness. Reported prevalence rates of AI in cirrhotic populations range broadly (10%–82%), depending on diagnostic criteria and testing methods**[12]**.

Despite indications that endocrine dysfunction may be clinically relevant in ACLF, endocrine failure is not currently encompassed in the EASL-CLIF criteria. These criteria emphasize organ failures that show a direct association with heightened mortality in ACLF. Introducing an additional category, such as endocrine failure, would require robust evidence that its evaluation offers prognostic benefits beyond existing classifications. Ongoing research could clarify the prognostic value of endocrine disturbances in ACLF; if a strong correlation emerges between endocrine failure and ACLF outcomes, this may warrant revisiting current diagnostic definitions. For now, however, the established organ failure criteria defined by the EASL-CLIF Consortium remain the primary focus.

Interactions Between the Pituitary-Adrenal Axis and Thyroid Hormones in ACLF

The relationship between the hypothalamic-pituitary-thyroid (HPT) axis and the hypothalamic-pituitary-adrenal (HPA) axis is pivotal in the development and progression of acute-on-chronic liver failure (ACLF). A thorough understanding of how these endocrine systems interact is essential for elucidating the complex hormonal imbalances seen in patients with ACLF. The hypothalamus acts as a central hub, coordinating signals from various bodily systems to maintain physiological balance. It regulates both the HPT and HPA axes through a combination of neural connections and hormone release from the pituitary gland. This dual regulatory mechanism enables the hypothalamus to effectively manage liver functions and overall metabolic processes by communicating with peripheral organs, including the liver, via autonomic nerves and hormonal pathways **[28].**

Within the HPA axis, the production of glucocorticoids plays a crucial role in liver function. Glucocorticoids influence several aspects of liver metabolism, such as gluconeogenesis, glycogen storage, and lipid processing. In individuals with ACLF, disruptions in the HPA axis can result in abnormal glucocorticoid levels, which may worsen liver dysfunction and accelerate the decline of liver health **[3]**.

Similarly, the HPT axis affects liver function by regulating thyroid hormone levels. Thyroid hormones are vital for normal liver metabolism, impacting processes like cholesterol production, fatty acid breakdown, and bile acid synthesis. In ACLF patients, changes in thyroid hormone concentrations are frequently observed and can interfere with these metabolic functions, further impairing liver performance **[26].**

The complex interaction between the HPT and HPA axes in ACLF highlights the intricate nature of endocrine regulation in liver diseases. Dysfunction in one of these axes can have repercussions on the other, leading to amplified effects on liver metabolism and overall bodily homeostasis. For example, variations in thyroid hormone levels can influence cortisol metabolism, while alterations in glucocorticoid levels can affect thyroid hormone activity. This bidirectional influence underscores the intertwined relationship between these endocrine systems in the context of ACLF **[3]**.

CONCLUSIONS

The dynamic interplay between the hypothalamic-pituitary-adrenal (HPA) axis and thyroid hormone metabolism plays a crucial role in the pathogenesis and progression of acute-on-chronic liver failure (ACLF). Endocrine dysfunctions, including adrenal insufficiency and non-thyroidal illness syndrome (NTIS), are prevalent in ACLF patients and are significantly associated with increased disease severity and mortality. These hormonal disruptions not only mirror the systemic impact of ACLF but also actively contribute to the exacerbation of multi-organ failure, underscoring their prognostic and therapeutic relevance. Clinically, the assessment of adrenal and thyroid function may enhance risk stratification and inform personalized treatment approaches, potentially improving patient outcomes.

However, the therapeutic modulation of the HPA axis and thyroid hormones in ACLF remains an area requiring further research to establish efficacy and safety. Future studies should focus on elucidating the precise pathways of endocrine dysregulation in ACLF and evaluating the benefits of targeted hormonal therapies. Integrating endocrine assessments into the comprehensive management of ACLF could offer a more holistic approach, ultimately contributing to better survival rates and enhanced quality of life for affected individuals.

The management of ACLF is challenging and requires a multidisciplinary approach. Early identification and treatment of precipitating factors, such as infections, are crucial. Supportive care, including renal replacement therapy for kidney failure and mechanical ventilation for respiratory failure, may be necessary. Liver transplantation remains the definitive treatment for selected patients with ACLF, although its applicability is limited by donor availability and patient suitability. In conclusion, ACLF is a severe syndrome characterized by the acute deterioration of liver function in patients with chronic liver disease, accompanied by multiple organ failures.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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