

Review: Adrenal Insufficiency in Liver Disease

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Abstract

Adrenal Insufficiency (AI), defined as deficient production or action of glucocorticoids resulting from either a structural damage of adrenal glands (primary adrenal insufficiency) or an impairment of the hypothalamic-pituitary axis (secondary adrenal disease), is being reported with increasing frequency in patients with liver disease, and some authors proposed the term “hepato-adrenal syndrome”. The prevalence of AI in patients with liver disease varies widely according to the study population: critically ill patients (33-92%), stable cirrhosis (31-60%), or decompensated cirrhosis, such as variceal bleeding (30-48%) and ascites (26-64%). However there is no current consensus about diagnostic criteria to define AI in patients with liver disease, and its prognostic relevance in stable cirrhosis is still unclear.

Keywords: Adrenal insufficiency; Liver; Cirrhosis

Introduction

Adrenal Insufficiency (AI) is defined as deficient production or action of glucocorticoids resulting from either a structural damage of adrenal glands, namely “primary adrenal insufficiency”, or an impairment of the hypothalamic-pituitary axis or “secondary adrenal disease” [1]. Primary AI is rare in general population, with an annual incidence of approximately 6/million adults/year and prevalence of 40 to 110 cases/million adults [2] and autoimmune diseases are the most frequent causes in developed countries. Long-term glucocorticoid therapy is the most frequent cause of secondary AI, however any process that impairs the ability of the hypothalamic-pituitary axis to secrete ACTH can cause secondary adrenal insufficiency (i.e. Pituitary or suprasellar tumors).

During critical illness (such as septic shock, severe community-acquired pneumonia, trauma, head injury, burns) AI is frequent, and is associated with a worse prognosis [3]. It has been described as Relative Adrenal Insufficiency (RAI), which is an inadequate glucocorticoid activity relative to the severity of illness.

Recently, AI is being reported with increasing frequency in patients with liver disease, and some authors proposed the term “hepato-adrenal syndrome” [4]. The prevalence of AI in patients with liver disease varies widely according to the study population: critically ill patients (33-92%) [4-8], stable cirrhosis (31-60%) [9-14] or decompensated cirrhosis, such as variceal bleeding (30-48-60%) [15]. However there is no current consensus to define AI in liver disease.

Diagnosis of Adrenal Insufficiency

Basal plasma cortisol

Basal plasma cortisol could be the initial test to assess AI. A very low early morning (measured between 8.00-9.00 am, coinciding with the diurnal peak of secretion) basal cortisol (less than 138 nmol/l) is highly suggestive of AI, but lacks sensitivity because most patients with adrenal insufficiency have cortisol levels exceeding this value, and dynamic tests need to confirm the diagnosis [2].

Basal ACTH levels

Basal ACTH levels (measured between 8-9 am) may differentiate between primary and secondary AI. In primary AI these exceed 100 pg/

ml (22 pmol/l), however, normal plasma ACTH values do not rule out mild secondary AI [16].

Insulin-induced hypoglycaemia test

Insulin-Induced Hypoglycaemia Test has been considered the gold standard, but is now rarely used due to concerns about patient safety when inducing hypoglycaemia.

Standard Synacthen Test (SST)

Standard Synacthen Test (SST) is the standard test to assess AI. SST is performed at any time irrespective of fasting with blood samples at baseline, and 30 and 60 minutes after 250 µg of ACTH 1-24 (Synacthen[®]) given intravenously or intramuscularly. A post-stimulation cortisol level >550 nmol/l (20 µg/dl) excludes primary AI [2].

Low Dose Short Synacthen Test (LDSST)

Low Dose Short Synacthen Test (LDSST) uses 1 µg of synthetic ACTH 1-24 (Synacthen[®]) given intravenously, with cortisol measured at baseline, and after 20 and 30 min. The normal response is a plasma cortisol concentration ≥ 500 nmol/l (18 µg/dl). LDSST is more sensitive than SST in patients without critical illness. However LDSST has not been validated in critically ill patients, or in acute hypothalamic-pituitary disorders [17].

Corticotrophin-Releasing Hormone (CRH) test

Corticotrophin-Releasing Hormone (CRH) test differentiates primary from secondary AI. In primary AI high basal ACTH levels rise after CRH administration. In secondary AI the low ACTH levels do not respond to CRH. Low ACTH levels with a prolonged increase after CRH define hypothalamic disease [2].

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Current Evidence for Adrenal Insufficiency Associated with Liver Disease

Critically ill patients with liver disease (Table 1)

First evidences for adrenal dysfunction associated with liver disease were found studying patients with acute liver injury or decompensation of chronic liver disease hospitalized in ICU setting.

Harry et al. [6] studied 45 consecutive patients with acute liver failure admitted to ICU: abnormal SST was found in 62% (reference ranges from a healthy population). The increment and peak cortisol values were lower in patients with hemodynamic instability, or ventilator dependence, and those who died or underwent liver transplantation.

Marik et al. [4] used the LDSST to assess adrenal function in 340 patients with either acute or chronic decompensated liver disease, or immediately after liver transplantation or transplanted previously requiring intensive care. AI was found in 33% fulminant hepatic failure, 66% chronic liver disease, 61% history of liver transplantation, and 92% recent liver transplantation (with a steroid-sparing immunosuppressive regimen). Low serum HDL cholesterol level was the only variable associated with AI. The authors proposed the term “hepato-adrenal syndrome” to describe the association between adrenal dysfunctions and liver disease. In another study, the same authors investigated the new onset of AI in 101 critically ill patients with acute or chronic liver disease without AI at admission, performing repeated LDSST tests: 16% developed AI at median of 3 days after initial testing. The only factor predicting AI was a low HDL level at admission ($p < 0.001$) [18]. The authors suggested that low levels of HDL may be pathogenetically linked to the high incidence of AI in patients with liver disease, because HDL is the principal precursor for steroid biosynthesis in the adrenal gland [19].

In another study [7] SST was performed to assess adrenal function

in 101 critically ill patients with cirrhosis and severe sepsis. AI was diagnosed in 52%, and was associated with lower mean arterial pressure (60 vs. 75 mmHg, $p < 0.001$), more required vasopressors (73% vs. 25%, $p < 0.001$), and increased hospital mortality rate (81% vs. 38%, $p < 0.001$). SST was also used to evaluate 25 consecutive patients with cirrhosis and septic shock [5]. The prevalence of AI was 68%, and it was higher in advanced liver disease (Child C: 76% vs. Child B: 25%, $p = 0.08$).

The discrepancies in the prevalence of AI (51-66%) shown in these studies may be due to differences in methodology and thresholds used to assess adrenal function. However these data show that AI in critically ill patients with liver disease is frequent and lead to a worse prognosis.

Patients with stable cirrhosis and decompensated cirrhosis (Table 2)

Several studies have shown a high prevalence of AI in not critically ill patients with cirrhosis, suggesting that AI is likely to be a feature of liver disease per se and not simply related to critical illness.

McDonald et al. [11] studied 38 patients with non-alcoholic liver disease and 40 healthy controls using both SST and IIT: compared with healthy controls, patients with liver disease had a 64% reduction in maximal increments of plasma cortisol after IIT and a 39% reduction after SST (all $p < 0.0001$), peak cortisol was negatively related to the severity of liver disease (assessed by Child-Pugh scores). In another study [13], the CRH test was used to study the HPA axes in 52 male cirrhotic: adrenal dysfunction was found in 42% using ACTH plasma level increments (< 2 times baseline), and in 58% using cortisol levels (peak value < 550 nmol/l or < 250 nmol/l increase). The HPA dysfunction was related to the severe liver disease, but was not influenced by aetiology of cirrhosis.

We investigated 101 patients with cirrhosis without infection or hemodynamic instability, using LDSST [9]. We found a high prevalence of AI (38%), related to the severity of liver disease. Low levels of

Authors	N. of patients and type of liver disease	Type of test performed and definition of AI	Prevalence of AI
Tsai et al. [7]	Chronic liver disease+Sepsis: 101	SST: baseline cortisol > 414 nmol/l, or cortisol increase > 250 nmol/l if baseline value between 414 and 918 nmol/l	51%
Harry et al. [6]	Acute Liver Failure: 45	SST: baseline cortisol > 250 nmol/L, cortisol increase > 250 nmol/L, or peak cortisol > 500 nmol/L	62%
Marik et al. [3]	Fulminant hepatitis: 24 Chronic liver disease: 146 Recent LT : 119 History LT: 51	LDSST: random cortisol level > 552 nmol/l in stressed patients (hypoxemic respiratory failure, shock, or requiring vasopressors), or random cortisol level > 414 nmol/l or peak cortisol > 552 nmol/l in non-stressed patients	66% 33% 92% 61%
Fernandez et al. [5]	Cirrhosis + Sepsis: 25	SST: baseline cortisol > 414 nmol/l, or cortisol increase < 250 nmol/l if baseline value between 414 and 918 nmol/l	63%

SST: Short Synacthen Test; LDSST: Low-Dose Short Synacthen Test

Table 1: Adrenal Insufficiency (AI) in critically ill patients with liver disease.

Authors	N. of patients with cirrhosis and aetiology	Type of test performed and definition of AI	Prevalence of AI (%)
McDonald et al. [11]	38 non-alcoholic liver disease compared with 40 healthy controls	IIT: reduction in maximal increments of plasma cortisol SST: reduction in maximal increments of plasma cortisol	64% 31%
Ziets et al. [13]	52 cirrhotics: 36 alcoholic, 16 virus related	CRH: a) rise of plasma ACTH < 2 times the baseline; b) peak cortisol value < 550 nmol/l or an increase < 250 nmol/l	42% 58%
Fede et al. [9]	101 cirrhotics: 29 alcoholic; 47 viral; 29 other	LDSST: a) peak serum cortisol < 494 nmol/l ; b) peak serum cortisol < 442 nmol/l; c) delta cortisol < 250 nmol/l	38% 29% 60%
Acevedo J et al. [20]	143 non-critically ill patients with cirrhosis	RAI was defined as a serum total cortisol increase < 9 µg/dL after SST from basal values < 35 µg/dL	26%

IIT: Insulin-Induced Hypoglycaemia Test; SST: Short Synacthen Test; LDSST: Low-Dose Short Synacthen Test; RAI: Relative Adrenal Insufficiency.

Table 2: Adrenal Insufficiency (AI) in patients with stable cirrhosis.

morning basal cortisol (between 8.00-9.00 AM) were an independent risk factor for AI.

LDSST and SST were used in 20 patients with cirrhosis and variceal bleeding, 60 stable cirrhotics and 14 healthy volunteers [15]. The prevalence of AI was similar in bleeders and stable cirrhotics using SST, but with LDSST it was higher in bleeders (60% vs. 48%; $p=0.01$). Furthermore, variceal bleeders had higher basal and peak cortisols than stable cirrhotic, but similar delta cortisol, demonstrating an inadequate adrenal response with respect to the severity of patient illness (critical illness-related corticosteroid insufficiency). AI was not associated with significant differences in clinical course/outcomes. Lastly, in a recent study assessing 143 non-critically ill patients with cirrhosis, low total delta cortisol values have been associated with higher incidence of severe sepsis, type 1 hepatorenal syndrome, and higher short-term mortality [20].

Despite discrepancies in the prevalence of AI amongst studies, due to different criteria to define AI, the data demonstrate adrenal dysfunction in patients with stable and decompensated cirrhosis, not only due to sepsis but also bleeding and ascites.

Free cortisol vs. total cortisol measurement (Table 3)

A relevant issue in the assessment of AI in cirrhosis is the measurement of total serum cortisol rather than serum free cortisol. Normally, 70% of circulating cortisol is bound to Corticosteroid Binding Globulin (CBG), 20% is bound to albumin, whereas the remaining 10% is free or unbound. Only the latter is the biologically active fraction [21]. In patients with liver disease low albumina and CBG concentrations may increase the percentage of free cortisol, thus the prevalence of AI is overestimates if adrenal function is assessed only using total cortisol measurement. This has been demonstrated in several studies.

Galbois et al. [10] used salivary cortisol as a marker of free cortisol concentration to assess adrenal function in 88 patients with cirrhosis: 33% had an abnormal total cortisol levels but only 9% had AI when salivary cortisol was considered. Ascites and low HDL levels were independent risk factors for AI. In another study both serum total and plasma free cortisol were used to study 43 clinically stable cirrhotic [12]. The prevalence of AI was 39% using standard criteria (peak total cortisol<500 nmol/L), 47% using Critical Illness-Related Corticosteroid Insufficiency (CIRCI) criteria (delta total cortisol<250 nmol/L), and 12% using free cortisol criteria (peak plasma free cortisol<33 nmol/L). The low prevalence of AI found using free cortisol or salivary cortisol rather than total cortisol; lead some authors to express concerns about the clinical relevance of AI associated with cirrhosis [22].

We recently studied 79 patients with stable cirrhosis using both total and free cortisol measurements: AI was diagnosed in 34% of patients using total cortisol and in 29% using free cortisol [23]. Low concentrations of CBG mainly explained the discrepancy between the two cortisol assays. Moreover we evaluated the usefulness of estimated methods of free cortisol, i.e. calculated Free Cortisol (cFC) and Free Cortisol Index (FCI), which is the ratio between total cortisol and CBG concentration [24]. Measurements of cFC constantly overestimated free cortisol concentrations, with variations as large as 87%. Conversely, FCI had a good level of agreement with free cortisol.

Thus, this latter study showed a high prevalence of adrenal dysfunction in patients with cirrhosis independently of cortisol assays (free or total cortisol), and the FCI as useful surrogate of free cortisol to assess adrenal function in patients with liver disease. However these findings need to be validated with further studies.

Conclusion

The literature suggests that AI in patients with liver disease is frequent both during acute critical illness (sepsis, shock and variceal bleeding) and during stable cirrhosis [4-7]. Liver disease per se may lead to progressive impaired of HPA axis [9]. However, there needs to be consensus on the appropriate tests and the accepted normal values to assess adrenal function in liver disease.

The clinical presentation of AI may be subtle in the absence of an adrenal crisis, with the gradual development of nonspecific symptoms such as fatigue, weakness, diffuse myalgia, weight loss, nausea, anorexia [25]. In stable cirrhosis adrenal insufficiency could be a sub-clinical condition triggered by acute events such as infections or other acute illness, leading to a worse prognosis [9]. Basal total cortisol should be routinely measured when AI is highly suspected, and if there are low basal cortisol levels an ACTH stimulation test should be performed, to identify patients with AI and eventually corticosteroid supplementation needs to be considered, albeit the lack of clear recommendation in this regard.

The mechanisms by which liver disease leads to AI are still unclear, but some hypotheses have been suggested (Figure 1). A decrease in total cholesterol, HDL cholesterol, and LDL cholesterol concentrations, frequent in cirrhosis [26], may lead to lack of substrates for steroidogenesis [19] and to a progressive exhaustion of adrenal reserve ("Adrenal-exhaustion syndrome") [18]. Furthermore, the increased levels of circulating endotoxin (e.g. lipopolysaccharide) and pro inflammatory cytokines (such as TNF- α , IL-1, and IL-6) frequent during liver disease could impair the HPA axis [27].

Authors	No. of patients with cirrhosis and aetiology	Type of test performed and definition of AI	AI%
Galbois et al [10]	88 (ALD: 63, VIR: 63, ALD+VIR: 8, other: 4)	SST a) basal serum total cortisol<250 nmol/l or/and post-stimulation values<494 nmol/l or/and increase values<250 nmol/l b) basal salivary cortisol<1.8 ng/ml or/and post-stimulation values<12.7 ng/ml or/and increase values<3 ng/ml	33% 9%
Tan et al. [12]	43 (ALD: 10, VIR: 11, ALD + HCV: 8, PBC: 3, PSC: 4, NASH: 4, Other: 3) 10 healthy volunteers	SST a) peak total cortisol<500 nmol/l b) delta total cortisol<250 nmol/l c) peak plasma free cortisol<33 nmol/l	39% 47% 12%
Fede et al. [9]	79 (ALD: 44, VIR: 14, other: 21)	LDSST a) peak serum cortisol<494 nmol/l b) peak free cortisol<33 nmol/l c) peak free cortisol<25 nmol/l	34% 28% 19%

SST: Short Synacthen Test; LDSST: Low-Dose Short Synacthen Test.

Table 3: Adrenal Insufficiency (AI) in patients with cirrhosis using total cortisol, free cortisol and salivary cortisol.

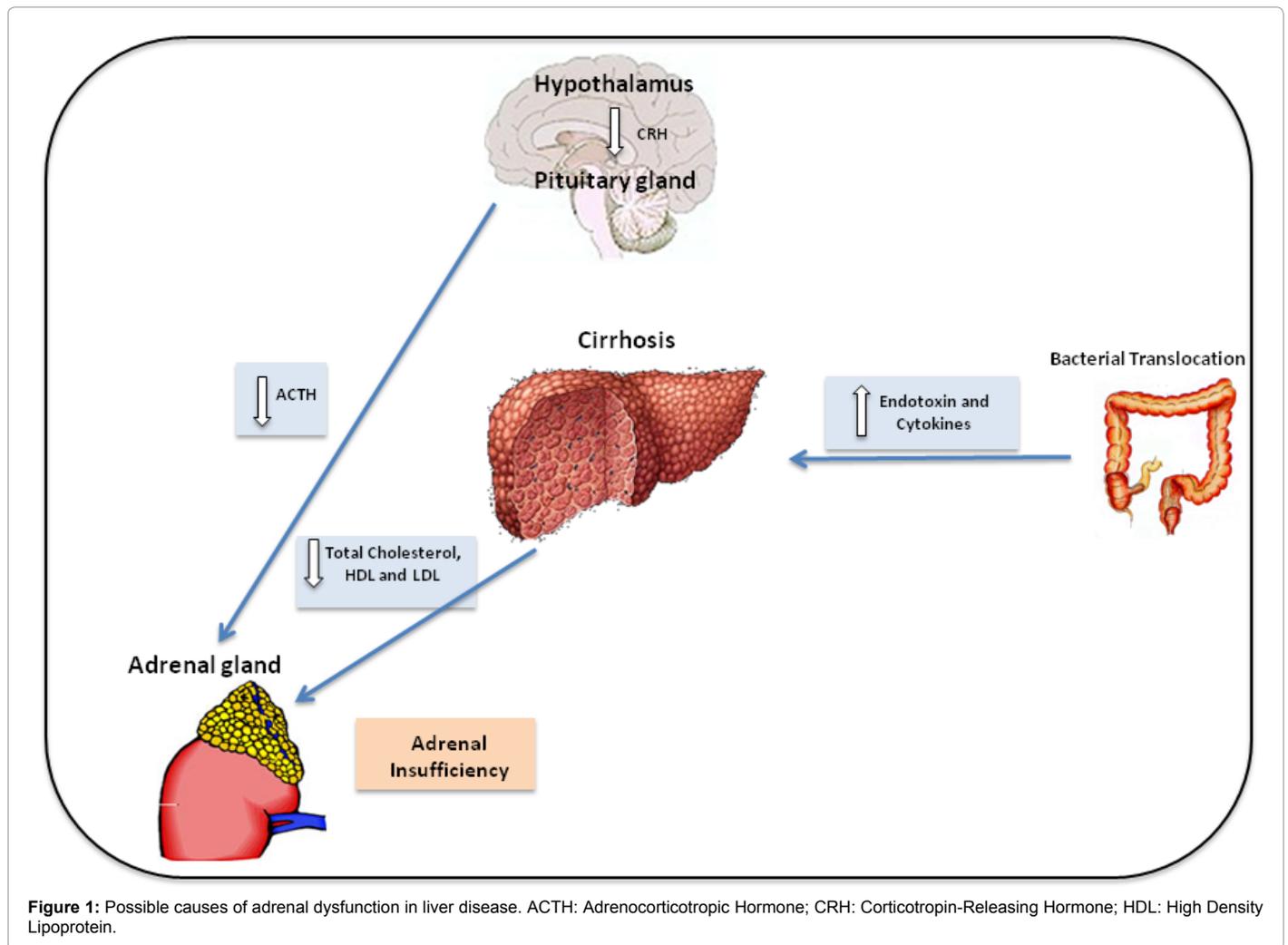


Figure 1: Possible causes of adrenal dysfunction in liver disease. ACTH: Adrenocorticotropic Hormone; CRH: Corticotropin-Releasing Hormone; HDL: High Density Lipoprotein.

Further studies are needed to clarify the clinical importance of AI associated to liver disease. Lastly, the effect of corticosteroid supplementation in patients with liver disease and acute decompensation or critical events should be assessed prospectively within randomized clinical trials.

Contributorship Statement

Fede Giuseppe: conception and design, acquisition of data, analysis and interpretation of data, drafting the article; Luisa Spadaro: revising the article critically for important intellectual content; Francesco Purrello: revising the article critically for important intellectual content.

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