REVIEW

Adrenocortical Dysfunction in Liver Disease: A Systematic Review

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In patients with cirrhosis, adrenal insufficiency (AI) is reported during sepsis and septic shock and is associated with increased mortality. Consequently, the term "hepato-adrenal syndrome" was proposed. Some studies have shown that AI is frequent in stable cirrhosis as well as in cirrhosis associated with decompensation other than sepsis, such as bleeding and ascites. Moreover, other studies showed a high prevalence in liver transplant recipients immediately after, or some time after, liver transplantation. The effect of corticosteroid therapy in critically ill patients with liver disease has been evaluated in some studies, but the results remain controversial. The 250-μg adreno-cortico-tropic-hormone stimulation test to diagnose AI in critically ill adult patients is recommended by an international task force. However, in liver disease, there is no consensus on the appropriate tests and normal values to assess adrenal function; thus, standardization of normal ranges and methodology is needed. Serum total cortisol assays overestimate AI in patients with cirrhosis, so that direct free cortisol measurement or its surrogates may be useful measurements to define AI, but further studies are needed to clarify this. In addition, the mechanisms by which liver disease leads to adrenal dysfunction are not sufficiently documented. This review evaluates published data regarding adrenal function in patients with liver disease, with a particular focus on the potential limitations of these studies as well as suggestions for future studies. (HEPATOLOGY 2012;55:1282-1291)

In patients with cirrhosis, adrenal insufficiency (AI) during critical illness is associated with increased mortality,[1,2] leading to what is termed "hepato-adrenal syndrome".[3] AI is frequent in stable and in decompensated cirrhosis without sepsis, such as variceal bleeding (30%-48%) and ascites (26%-64%).[4,5] AI is documented early[3] and late[6] after liver transplantation. Beneficial effects of corticosteroid therapy during sepsis and shock in cirrhosis are reported,[3,7-9] but one recent randomized, controlled trial has shown no benefit.[7]

However, there are some limitations in assessing hypothalamus-pituitary-adrenal (HPA) function in cirrhosis resulting from methodological problems of adreno-cortico-tropic-hormone (ACTH) stimulation tests.[10] Moreover, AI is overestimated in cirrhosis using total cortisol, rather than free cortisol, assays because of low levels of cortisol-binding protein.

This review evaluates published data regarding adrenal function in patients with cirrhosis, focusing on potential limitations, including problems in assessing adrenal function, with suggestions for future studies.

Identification of Studies

We searched MEDLINE, Cochrane Controlled trial Register (CENTRAL), EMBASE, and Science Citation

Abbreviations: ACTH, adreno-cortico-tropic-hormone; AI, adrenal insufficiency; ALF, acute liver failure; CBG, corticosteroid-binding globulin; CIRCI, critical illness-related corticosteroid insufficiency; CLD, chronic liver disease; CRH, corticotrophin-releasing hormone; FAGA, functional adrenal gland atrophy; FCI, free cortisol index; HDL, high-density lipoprotein; HPA, hypothalamus-pituitary-adrenal; ICU, intensive care unit; IIT, insulin-induced hypoglycemia test; IL, interleukin; IV, intravenously; LDL, low-density lipoprotein; LDSST, low-dose short Synacthen test; LT, liver transplant; MAP, mean arterial pressure; MELD, model for end-stage liver disease; PBC, primary biliary cirrhosis; RAI, relative adrenal insufficiency; RR, relative risk; SST, Short Synacthen test; TNF-a, tumor necrosis factor alpha.

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Index databases until April 2011 as well as published abstracts in the last 2 years, using the key words "adrenal insufficiency" and "liver disease" and their synonyms (see details in Supporting Materials and Methods), without language restrictions.

We could evaluate 23 studies (16 full-text, 5 abstracts, and 2 case reports) of 12,696. G.F. and G.G. independently screened studies identified by the search, then verified them reciprocally. Disagreements were arbitrated by A.K.B.

Definition of AI

AI is defined as deficient production or action of glucocorticoids resulting from either a structural damage of adrenal glands, "primary adrenal failure," or an impairment of the hypothalamic-pituitary axis or "secondary adrenal disease."[11]

In critically ill patients, there is relative adrenal insufficiency (RAI), which is an inadequate glucocorticoid activity relative to the severity of illness. This term has been replaced by critical illness-related corticosteroid insufficiency (CIRCI), which is a reduced adrenal steroid production or tissue resistance to glucocorticoids in patients with systemic inflammation.[12]

AI could be a feature of liver disease *per se* (i.e., hepato-adrenal syndrome).[3] However, there is no current consensus defining AI in liver disease.

Laboratory Assessment of HPA Axes

Basal Plasma Cortisol. A basal plasma cortisol level <138 nmol/L (5 μg/dL) (measured between 8:00 a.m. and 9:00 a.m.) is highly suggestive of AI. When levels are >415 nmol/L (15 μg/dL), AI is unlikely. AI requires confirmation by dynamic tests.[13]

Basal Plasma ACTH. Basal plasma ACTH levels (measured between 8:00 a.m. and 9:00 a.m.) exceed 100 pg/mL (22 pmol/L) in primary AI. Normal plasma ACTH values rule out primary, but not mild, secondary AI.[14]

Insulin-Induced Hypoglycemia Test. The insulin-induced hypoclycemia test (IIT) assesses the HPA axis. When hypoglycemia is achieved after insulin (usually between 30 and 45 minutes), plasma cortisol levels should exceed 500-550 nmol/L (18-20 μg/dL). However, this test is contraindicated in elderly patients, subjects with seizure disorders, or cardiovascular disease, so it has very limited use.[13]

Short Synacthen Test. The Short Synacthen Test (SST) is the standard test to assess AI. It is performed at any time irrespective of fasting with blood samples at baseline, 30 and 60 minutes after 250 μg of ACTH (1-24) (Synacthen), and is given intravenously (IV) or intramuscularly. A poststimulation cortisol level >550 nmol/L (20 μg/dL) excludes primary AI.[13]

Low-Dose Short Synacthen Test. The low-dose short Synacthen test (LDSST) uses 1 μg of synthetic ACTH (1-24) (Synacthen) given IV, with cortisol measured at baseline and after 20 and 30 minutes. Normal response is a plasma cortisol concentration ≥500 nmol/L (18 μg/dL). The LDSST is more sensitive than the SST in patients without critical illness. However, the LDSST has not been validated in critically ill patients or in acute hypothalamic-pituitary disorders.[15]

Corticotrophin-Releasing Hormone Test. The 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.[13]

AI in Critical Illness. An international task force defines AI in critical illness by a delta cortisol level (i.e., difference between basal and poststimulation cortisol) of 250 nmol/L (9 μg/dL) after SST or a random total plasma cortisol level of 276 nmol/L (10 μg/dL).[12]

Current Evidence for Adrenocortical Dysfunction Associated With Liver Disease

Critically Ill Patients With Liver Disease. Adrenal function was studied in 45 consecutive patients with acute hepatic dysfunction admitted to the intensive care unit (ICU)[4]: 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. Despite this definition of AI, which could lead to overestimating its prevalence, the latter was similar to that of other studies with similar patients (Table 1).

The LDSST was used to evaluate 340 patients with either acute or acute decompensated chronic liver disease or immediately after liver transplantation or transplanted previously requiring intensive care.[3] AI was found in 33% of patients with fulminant hepatic failure, 66% of patients with chronic liver disease (CLD), 61% with history of liver transplantation, and 92% with recent liver transplantation (with a steroid-sparing immunosuppressive regimen). There were no

Table 1. AI in Critically Ill Patients With Liver Disease

Investigators (Reference)	No. of Patients and Type of Liver Disease	Type of Test Performed and Definition of AI	AI%	Main Finding and Outcomes
Harry et al., 2002	ALF: 45	SST: baseline cortisol <250 nmol/L, delta cortisol* <250 nmol/L, or peak cortisol† <500 nmol/L	62	Lower delta cortisol* ($P < 0.001$) and peak cortisol† ($P < 0.001$) in patients with hemodynamic instability, with ventilator dependence ($P < 0.01$ and $P < 0.01$), and in those who died or underwent LT ($P < 0.01$ and $P < 0.01$)
Marik et al., 2005	Fulminant hepatitis: 24 CLD: 146 Recent LT: 119 History of LT: 51	LDSST: random cortisol level <552 nmol/L in stressed patients (i.e., patients with hypoxemic respiratory failure, with systolic blood pressure <90 mmHg, or requiring vasopressor agents), or random cortisol level <414 nmol/L or peak cortisol† <552 nmol/L in nonstressed patients	33 66 92 61	Low serum HDL cholesterol level was the only laboratory variable predictive of AI.
Tsai et al., 2006	Cirrhosis+sepsis: 101	SST: baseline cortisol <414 nmol/L, or delta cortisol* <250 nmol/L, if baseline value between 414 and 918 nmol/L	51	Cortisol response to the SST was inversely correlated with Child–Pugh and MELD scores, SOFA, APACHE III, and OSF number. Lower MAP (60 versus 75 mm Hg; $P < 0.001$), higher vasopressor dependency (73% versus 24.48%; $P < 0.001$), and higher hospital mortality rate (80.76% versus 36.7%; $P < 0.001$) in patients with AI
Fernández et al., 2006	Cirrhosis+sepsis: 25	SST: baseline cortisol <414 nmol/L, or delta cortisol* <250 nmol/L if baseline value between 414 and 918 nmol/L	63	AI was more frequent in patients with advanced cirrhosis (Child-Pugh C [76%] versus Child-Pugh B [25%]; $P = 0.08$)

Abbreviations: OSF, organ system failure; SOFA, sequential organ failure assessment; APACHE, acute physiology age chronic health evaluation.
*Delta cortisol: difference between peak and basal total cortisol.
†Peak cortisol: cortisol concentration 60 minutes after corticotropin stimulation.

differences in severity of liver disease between patients with or without AI. Low serum high-density lipoprotein (HDL) cholesterol level was the only variable predictive of AI. The term "hepato-adrenal syndrome" was proposed. New onset of AI was evaluated in 101 critically ill patients[16] with acute liver disease or CLD without AI at admission, performing repeated LDSST tests: 16% developed AI at a median of 3 days after initial testing. The only factor predicting AI was a low HDL level at admission ($P < 0.001$). However, the SST is the recommended test to study adrenal function in critically ill patients, and the LDSST may be not be appropriate because of a lack of published data.[12] The LDSST probably led to misdiagnosing AI and accounts for the lack of correlation between AI and severity of liver disease shown in other similar studies (Table 1).

The SST was also used to study 101 critically ill patients with cirrhosis and severe sepsis.[5] AI was diagnosed in 52% and was related to severity of liver disease, using model for end-stage liver disease (MELD) and Child-Pugh scores. In patients with AI, mean arterial pressure (MAP) was lower (60 versus 75 mmHg; $P < 0.001$), more required vasopressors (73% versus 25%; $P < 0.001$), and hospital mortality rate was increased (81% versus 38%; $P < 0.001$).

The SST was also used to evaluate 25 consecutive patients with cirrhosis and septic shock.[8] The prevalence of AI was 68% and was higher in advanced liver disease (Child-Pugh C [76%] versus Child-Pugh B [25%]; $P = 0.08$).

Although differences in methodology and thresholds used to define AI in these studies may explain discrepancies in the prevalence of AI (51%-66%), all studies show that AI in critically ill patients with liver disease is frequent. Thus, there is indirect evidence that critical illness-related corticosteroid insufficiency (CIRCI) exists, but it should be diagnosed using the recently recommended criteria.[12]

Patients With Cirrhosis, Not Critically Ill. The SST and IIT were both used to assess HPA function in 38 patients with nonalcoholic liver disease and 40 healthy controls (Table 2).[17] Compared to 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 $P < 0.0001$). There was a significant negative correlation with both tests between severity of liver disease (assessed by Child-Pugh scores) and peak cortisol responses. The greater impairment of adrenocortical response to central HPA axis stimulation (IIT) suggested a

Table 2. AI in Patients With Cirrhosis, Not Critically Ill

Investigators (Reference)	No. of Patients With Cirrhosis and Etiology	Type of Test Performed and Definition of AI	AI%	Main Finding and Risk Factor for AI
McDonald et al., 1993	38 nonalcoholic liver disease 40 healthy controls	IIT: reduction in maximal increments of plasma cortisol SST: reduction in maximal increments of plasma cortisol	64 31	Negative correlation between Child-Pugh scores and peak cortisol
Zietz et al., 2003	52 (ALD: 36; VIR: 16)	CRH (1) rise of plasma ACTH <twice the baseline (2) peak cortisol value <550 nmol/L or an increase <250 nmol/L	 42 58	HPA dysfunction more evident in patients with advanced liver disease (Child-Pugh B and C)
Galbois et al., 2010	88 (ALD: 63; VIR: 63; ALD+VIR: 8; other: 4)	SST (1) basal serum total cortisol <250 nmol/L and/or peak total cortisol† <494 nmol/L and/or delta cortisol‡ <250 nmol/L (2) basal salivary cortisol <1.8 ng/mL and/or post-stimulation values <12.7 ng/mL and/or increase in values <3 ng/mL	 33 9	Low HDL level was the only independent risk factor for AI. Hypoalbuminemia (albumin <25 g/L) was the only factor associated with a discrepancy between serum total cortisol and salivary cortisol measurement in diagnosing AI.
Tan et al., 2010	43 patients (ALD: 10; VIR: 11; ALD+HCV: 8; PBC: 3; PSC: 4; NASH: 4; other: 3) and 10 healthy volunteers (1) peak total cortisol† <500 nmol/L (2) delta cortisol‡ <250 nmol/L (3) peak plasma free cortisol <33 nmol/L	SST 39 47 12		AI group according to free cortisol criteria had higher MELD scores (19 ± 3.2 versus 13 ± 0.8; $P = 0.03$) and higher mortality rate (60% versus 5%; $P < 0.001$). AI group, according to total cortisol criteria, had comparable severity of liver disease compared to patients without AI.
Fede et al., 2011	101 (ALD: 29; VIR: 47; other: 29)	LDSST (1) peak serum cortisol† <494 nmol/L (2) peak serum cortisol† <442 nmol/L (3) delta cortisol‡ <250 nmol/L	 38 29 60	AI group had more advanced liver disease (Child-Pugh score: 10 versus 7, $P < 0.0001$; MELD score: 17 versus 12, $P < 0.0001$). INR ($P = 0.01$), ascites ($P = 0.04$), and basal cortisol ($P = 0.01$) were independently associated with AI.
Thevenot et al, 2011	125 "consecutive," 95 nonseptic, and 30 septic patients	SST peak cortisol† <510 nmol/L	7.2	AI group had more severe liver disease (MELD score: 25 versus 17; $P = 0.0078$), but similar basal salivary cortisol and serum-free cortisol concentrations, compared to those with normal adrenal response.
Acevedo et al., 2010*	10 with compensated cirrhosis, compared to 188 with cirrhosis associated with SBP, non-SBP infections, noninfected ascites, hepatic encephalopathy, gastrointestinal bleeding, hepatorenal syndrome, and shock	Criterion 1: basal cortisol <414 nmol/L and/or delta cortisol‡ <250 nmol/L; criterion 2: delta cortisol‡ <250 nmol/L	64 27	The prevalence of RAI was not significantly different between compensated and decompensated cirrhosis. Moreover, mortality was not different among patients with or without AI.
Acevedo et al., 2011*	166 with advanced cirrhosis	RAI: delta cortisol‡ <250 nmol/L after SST	26	AI group presented more severe circulatory dysfunction (MAP: 77 versus 82, $P = 0.04$; serum sodium <130 mEq/L: 44% versus 21%; $P = 0.01$), higher probability of developing severe infections (23% versus 9%; $P = 0.01$) and septic shock (17% versus 2%; $P = 0.01$) during hospitalization, and higher hospital mortality (19% versus 7%; $P = 0.04$).
Risso et al., 2011*	85 with ascites (without sepsis or shock)	AI: delta cortisol‡ <250 nmol/L and/or peak cortisol† <494 nmol/L after SST	39	After a median follow-up of 198 days, there was higher mortality in AI group (33% versus 10%; $P < 0.05$). In the multivariate analysis, AI was significantly associated with reduced survival ($P = 0.03$).

Table 2. *Continued*

Investigators (Reference)	No. of Patients With Cirrhosis and Etiology	Type of Test Performed and Definition of AI	AI%	Main Finding and Risk Factor for AI
Graupera et al., 2010*	37 with severe acute bleeding	RAI: basal cortisol <414 nmol/L or delta cortisol‡ <250 nmol/L after SST	38	RAI was associated with higher risk of therapeutic failure to control bleeding at day 5 (22% versus 43%; $P = 0.04$) and a lower survival at 6 weeks (31% versus 64%; $P = 0.05$), although no differences in overall survival were observed.
Triantos et al., 2011	20 with variceal bleeding, compared to 60 with stable cirrhosis and 14 healthy volunteers	(1) SST: peak serum cortisol† <494 nmol/L in stable cirrhosis or delta cortisol‡ <250 nmol/L or a total basal cortisol <276 nmol/L in variceal bleeding	30	Variceal bleeders had a higher basal and peak cortisol† than stable cirrhotics, but similar delta cortisol.‡ AI was not associated with significant difference regarding the clinical course/outcomes.
		(2) LDSST: peak serum cortisol† <494 nmol/L in stable cirrhosis or delta cortisol‡ <250 nmol/L or a peak cortisol† <690 nmol/L in variceal bleeding	30 48	

Abbreviations: ALD, alcoholic liver disease; VIR, viral cirrhosis; HCV, hepatitis C virus; PSC, primary sclerosing cholangitis; NASH, nonalcoholic steatohepatitis; INR, international normalized ratio; SBP, spontaneus bacterial peritonitis.
*Meeting abstract.
†Peak cortisol: cortisol concentration 60 minutes after corticotropin stimulation.
‡Delta cortisol: difference between peak and basal total cortisol.

predominantly hypothalamic-pituitary dysfunction, rather than intrinsic adrenal gland impairment.[17]

The CRH test was used to study the HPA axes in 52 male cirrhotics.[18] The HPA axis was abnormal in 42% using ACTH plasma level increments (less than twice baseline) and in 58% using cortisol levels (peak value, <550 or <250 nmol/L increase). HPA dysfunction was more evident with more severe liver disease, but was not influenced by etiology of cirrhosis.

AI was assessed in 88 patients with cirrhosis, using salivary cortisol as a marker of free cortisol concentration[19]: 33% had an abnormal SST, but only 9% had AI when salivary cortisol was considered. Ascites and low HDL levels were independent risk factors for AI. The high proportion with alcoholic cirrhosis (72%, with only 22% weaned from alcohol for more than 6 months) could have led to the relatively low prevalence of AI, because alcohol stimulates adrenal cortisol synthesis.[20]

A clear relationship to the severity of liver disease could not be shown, because many patients had infection (27%), systemic inflammatory response syndrome (43%), or sepsis (16%), and infection can affect adrenal function.

Both serum total and plasma free cortisol were used to study 43 clinically stable cirrhotics.[21] The prevalence of AI was 39% using standard criteria (peak total cortisol, <500 nmol/L), 47% using CIRCI criteria (delta total cortisol, <250 nmol/L), and 12% using free cortisol criteria (peak plasma free cortisol, <33 nmol/L). However, CIRCI criteria are recommended only with critical illness[12]; it is not known whether they are applicable in stable cirrhosis. Moreover, the value of 33 nmol/L for peak free plasma cortisol has not been validated for diagnosis of AI in liver disease, although this is the lowest published limit of plasma free cortisol in healthy subjects.[22]

We recently investigated 101 patients with cirrhosis without infection or hemodynamic instability using LDSST.[23] We found a high prevalence of AI (38%) related to the severity of liver disease. Low levels of morning basal cortisol (between 8:00 a.m. and 9:00 a.m.) were an independent risk factor for AI.

RAI, defined as basal total cortisol level <414 nmol/L and/or delta cortisol level <250 nmol/L (criterion 1) or as a delta cortisol level <250 nmol/L (criterion 2) after SST, was assessed in 10 patients with compensated cirrhosis, compared with 188 patients with cirrhosis and complications, including SBP, other infections, ascites, hepatic encephalopathy, gastrointestinal bleeding, hepatorenal syndrome, and shock.[24] RAI was 64% using criterion 1 and 27% using

criterion 2, but was similar between compensated and decompensated cirrhosis. Mortality was similar between patients with or without AI.

The same group assessed RAI (delta cortisol, <250 nmol/L after SST) in 166 patients with advanced cirrhosis[25]: 26% had RAI. Patients with RAI had more severe circulatory dysfunction (MAP, 77 versus 82 mmHg; $P = 0.04$), lower serum sodium levels (<130 mEq/L; $P = 0.01$), more severe infections ($P = 0.01$), septic shock ($P = 0.01$), and increased hospital mortality ($P = 0.04$).

The SST was used to assess 85 patients with cirrhosis and noninfected ascites.[5] AI was present in 39% and was independently associated with higher mortality (33% versus 10%; $P < 0.05$).

In acute variceal bleeding and cirrhosis, RAI was found in 14 of 37 (38%) patients.[26] RAI was associated with higher risk of failure to control bleeding at day 5 ($P = 0.04$) and a lower survival at 6 weeks ($P = 0.05$), although no differences in overall survival were observed.

The LDSST and SST were used in 20 patients with cirrhosis and variceal bleeding, 60 stable cirrhotics, and 14 healthy volunteers.[4] The prevalence of AI was similar in bleeders and stable cirrhotics using the SST, but with the LDSST, it was higher in bleeders (60% versus 48%; $P = 0.01$). Furthermore, variceal bleeders had higher basal and peak cortisol levels than stable cirrhotics, but similar delta cortisol levels, demostrating an inadequate adrenal response with respect to the severity of patient illness (i.e., CIRCI). AI was not associated with significant differences in clinical course or outcomes.

Despite discrepancies in the prevalence of AI among studies, because of different criteria to define AI, the data demonstrate adrenal dysfunction in patients with stable and decompensated cirrhosis not only resulting from sepsis, but also from bleeding and ascites. Thus, AI is likely to be a feature of liver disease *per se* and not simply related to critical illness. However, there needs to be a consensus on the appropriate tests and the accepted normal values to assess adrenal function in liver disease. The mechanisms and the clinical importance of HPA dysfunction during liver disease also need to be explored further.

Liver Transplant Recipients. AI has been reported after liver transplant (LT) in patients treated with steroid-free immunosuppression[27] or after suspension of steroids.[28]

Using the LDSST, a very high prevalence (92%) of AI was reported in 119 patients after LT who were maintained on steroid-free immunosuppressive regimens.[3] However, the LDSST is not appropriate in this high-stress condition after major surgery, and the SST should have been used.[12] Again, this probably led to overestimating RAI. RAI was less prevalent (61%) in 51 LT patients studied some time after LT.[3]

Glucocorticoids, used in most immunosuppressive protocols after LT, prevent LT recipients from developing early RAI. However, prolonged use of corticosteroids can lead to HPA axis suppression and, in some cases, to functional adrenal gland atrophy (FAGA).[6]

Adrenal function in 87 LT recipients was evaluated using the SST before complete steroid withdrawal.[6] FAGA was present in 27%. FAGA was correlated with both length and cumulative dosage of corticosteroids and total cholesterol and ACTH concentrations. However, no data were available on adrenal function before LT.

In 90 consecutive patients undergoing first elective LT in our unit,[29] intraoperative administration of 1,000 mg of methylprednisolone was associated with significant reduced requirements for fluid administration, vasopressors, renal replacement therapy, invasive ventilation, and ICU stay, compared to patients not receiving the bolus. These data suggest probable AI as well as benefit from giving intraoperative steroids during LT.

Adrenal dysfunction may be subclinical during liver disease.[23] Factors associated with LT, such as hypotension, infection, and severe blood loss, may induce acute AI in the early postoperative period. Long-term corticosteroid immunosuppression can lead to FAGA.[6] Further studies are needed to explore the clinical relevance of AI in patients undergoing LT.

Corticosteroid Supplementation in Patients With Liver Disease

Currently, corticosteroids are used for patients with septic shock, particularly with a poor response to fluids and vasopressors.[12] In critically ill patients with liver disease, there are few published data (Table 3).

The effect of 300 mg of hydrocortisone/day in 20 vasopressor-dependent patients with acute liver failure (ALF) or "acute-on-chronic liver failure" was compared to a historical control group without steroids.[9] Steroid use was associated with reduction in vasopressor doses, but no survival benefit. Notably, corticosteroids were associated with more infections, especially with resistant organisms.

An evaluation of 100 mg/8 hours of hydrocortisone IV was done in 140 vasopressor-dependent patients with acute liver disease or CLD[3]: Norepinephrine

Table 3. Published Studies Reporting on Hydrocortisone Therapy in Patients With Liver Disease

Investigators (Reference)	No. of Treated Patients and Type of Liver Disease	Steroid Dose	Outcomes Associated With Steroid Treatment
Harry et al., 2003	20 vasopressor-dependent patients with ALF or acute on chronic liver failure	Hydrocortisone: 300 mg/day	Reduction in vasopressor doses, but no survival benefit; higher incidence of infection
Marik et al., 2005	140 vasopressor-dependent patients with acute liver disease or CLD	Hydrocortisone: 100 mg/8 hours	Reduction in the dose of norepinephrine at 24 hours in adrenal insufficiency group ($P = 0.02$), but not in nonadrenal insufficiency group ($P = 0.62$). In adrenal insufficiency group, treatment with hydrocortisone was associated with a lower mortality rate (26% versus 46%; $P = 0.002$)
Fernández et al., 2006	17 consecutive cirrhotics with septic shock and RAI	Hydrocortisone: 50 mg/6 hours	Resolution of septic shock (96% versus 58%; $P = 0.001$), survival in the ICU (68% versus 38%; $P = 0.03$), and hospital survival (64% versus 32%; $P = 0.003$)
Arabi et al., 2010*	39 patients with cirrhosis and septic shock	Hydrocortisone: 50 mg/6 hours	Reduction in vasopressor doses and higher rate of shock reversal (RR, 1.5, 95% CI: 0.98-2.55; $P = 0.05$); no benefit in 28-day mortality; increase in shock relapse (RR, 2.58; 95% CI: 1.04-6.45; $P = 0.03$) and gastrointestinal bleeding (RR, 3; 95% CI: 1.08-8.36; $P = 0.02$).

Abbreviation: CI, confidence interval.
*Randomized, controlled trial.

dosage at 24 hours was reduced ($P = 0.02$) in patients with AI, whereas without AI, hydrocortisone had no effect. Among patients with AI, hydrocortisone was associated with reduced mortality (26% versus 46%; $P = 0.002$), but this was not assessed prospectively.

The effects of 50 mg/6 hours of hydrocortisone in 17 consecutive cirrhotics with septic shock and RAI was assessed prospectively, compared to a historical cohort of 50 consecutive patients with cirrhosis and septic shock, in whom adrenal function was not investigated and did not receive steroids.[8] Resolution of septic shock (96% versus 58%; $P = 0.001$), survival in intensive care (68% versus 38%; $P = 0.03$), and hospital survival (64% versus 32%; $P = 0.003$) were significantly higher in the treated group.

The first randomized, controlled trial evaluating low-dose hydrocortisone in patients with cirrhosis and septic shock[7] showed that hydrocortisone, given until shock resolution, was associated with a significant reduction in vasopressor doses and a higher rate of shock reversal (relative risk [RR], 1.5; $P = 0.05$), but it did not reduce 28-day mortality. Hydrocortisone was associated with increased shock relapse (RR, 2.58; $P = 0.03$) and gastrointestinal bleeding (RR, 3.0; $P = 0.02$). Interestingly, when patients were stratified by SST response, hemodynamic improvement was observed only in the 76% of patients with RAI. Thus, RAI may be inherently present in cirrhosis and not reflect a temporary sepsis-related phenomenon. If this is the case, a longer duration of steroid therapy might be required. Alternatively, stress doses of hydrocortisone may further suppress the HPA axis and thus rapid tapering could precipitate an adrenal crisis, accounting for the high rate of shock relapse after hydrocortisone. This could mask the benefits of therapy.

These preliminary data suggest possible beneficial effects of corticosteroid therapy during sepsis and shock in patients with liver disease, but further multicenter, randomized, controlled trials are needed. The clinical relevance of AI, both in stable cirrhosis and in critically ill patients, should be better studied to identify subgroups of patients that may benefit from corticosteroid supplementation.

Current Limitations in Assessing HPA Function in Patients With Liver Disease

ACTH Stimulation Tests. The SST has largely replaced the IIT as the first-line test to assess AI.[30] However, a recent National UK audit[10] showed some limitations in interpreting the SST, such as bias in analytical methods for serum cortisol, variability in defining normal ranges, and lack of clear protocols to perform the tests. The development of consensus guidelines should help to address these limitations.

Furthermore, there is concern that the SST, using a supraphysiological dose of 250 μg of corticotropin, can underestimate mild AI. Some evidence suggests that the LDSST (1 μg of corticotropin) represents a more physiological stimulus to the adrenal cortex as well as a more sensitive indicator of suboptimal

adrenal function.[15] Currently, the SST is recommended for diagnosing AI in critically ill adult patients,[12] but there are no clear recommendations in patients without critical illness.

The LDSST may be the appropriate test in patients with cirrhosis without critical illness, in whom an initial adrenal impairment may be subclinical. Conversely, the SST could be better for liver disease and acute decompensation. The appropriate ACTH test needs to be standardized in the various clinical settings.

Serum Total Versus Free Cortisol Concentrations. Normally, 70% of circulating cortisol is bound to corticosteroid-binding globulin (CBG), 20% is bound to albumin, and 10% exists as free cortisol. Only the latter is the biologically active form.[31] Low levels of CBG and overestimation of AI by total cortisol measurement have been demonstrated in noncirrhotic critically ill patients, especially if serum albumin level is <25 g/L.[32,33]

CBG was found to be significantly decreased in 47 cirrhotics, compared to 50 healthy controls (mean, 567 versus 859 nmol/L; $P < 0.0001$), and was lower in Child-Pugh C (344 nmol/L) than in Child-Pugh A (653 nmol/L) or B patients (618 nmol/L) ($P < 0.001$).[34] Moreover, CBG serum levels correlated inversely with Child-Pugh score ($r = -0.549$; $P < 0.001$). In another study, comparing 40 healthy volunteers and 38 patients with advanced liver disease, CBG serum levels were significantly reduced in the latter (mean, 614 versus 730 nmol/L).[17]

The free cortisol index (FCI) (ratio between total cortisol and CBG concentration) was used as the surrogate marker for free cortisol to assess AI in 15 patients with CLD and 11 with acute liver disease.[35] AI was found in 12 patients (46%) using total cortisol measurement (abnormal SST), but only 3 patients (13%) also had an FCI <12.

Salivary cortisol is another surrogate marker for free cortisol and its concentrations accurately reflect free cortisol concentrations in noncirrhotic patients, even with hypoalbuminemia or CBG abnormality.[36] In 88 patients with cirrhosis, salivary cortisol was used[19]: 33% had an abnormal SST according to serum total cortisol, but only 9% were categorized as having AI when salivary cortisol was considered. Hypoalbuminemia (albumin <25 g/L) was the only factor associated with discrepant results between the two types of estimation.

In another study,[21] total serum cortisol and plasma free cortisol were compared in 43 clinically stable cirrhotics and 10 healthy volunteers after SST. The prevalence of AI was discrepant (58% using total cortisol, compared to 12% using free cortisol). There was a significant correlation between total serum and plasma free cortisol and was stronger when serum albumin level was >30 g/L. In addition, measured free cortisol was compared with FCI and calculated free cortisol by Coolens' formula: There was poor agreement between the different sets of values (bias of 5.53, limits of agreement from −4.8 to 15.9 in Bland-Altman plots).

Last, in a recent study,[37] adrenal function was assessed in 125 consecutive cirrhotics (95 nonseptic and 30 septic patients), measuring basal and post-SST serum total cortisol as well as serum-free and salivary cortisol. Subnormal adrenal function was found in 7.2% of all patients: These patients mostly had severe liver disease, compared to those without AI (MELD score, 25 versus 17; $P = 0.0078$). However, patients with a subnormal SST response had similar basal salivary cortisol and serum-free cortisol concentrations, compared to those with normal adrenal response.

These data suggest that overestimation of AI in patients with liver disease is likely using total, rather than free, cortisol measurement. Although direct measurement of plasma free cortisol could be a more reliable marker of adrenal function in patients with low CBG levels, it is currently unsuitable for routine clinical practice because it is time consuming and expensive.[35] Moreover, the normal range of free cortisol to diagnose AI, in any setting of liver disease, is not defined. Salivary cortisol responses to ACTH stimulation may be a valid alternative, but more studies are needed to establish its diagnostic value in cirrhosis.[36] Previous or subclinical parotitis, particularly in alcoholic cirrhosis, and sicca syndrome in primary biliary cirrhosis (PBC) may affect the production of saliva, and in critically ill patients, blood contamination of saliva is likely, particularly if there is a bleeding tendency.

Summary and Perspectives

The literature suggests that HPA dysfunction in patients with liver disease is frequent, both during acute critical illness (e.g., sepsis, shock, and variceal bleeding) and during stable cirrhosis.[1-3,8] Liver disease *per se* may lead to progressive impairment of the HPA axis.[23] However, the prevalence of AI in different studies is discrepant and is probably the result of different criteria used to define AI. There needs to be a consensus on the appropriate tests and the accepted normal values to assess adrenal function in liver disease.

The mechanisms by which liver disease leads to HPA dysfunction have not been clarified, but some hypotheses have been suggested (Fig. 1). Cholesterol is

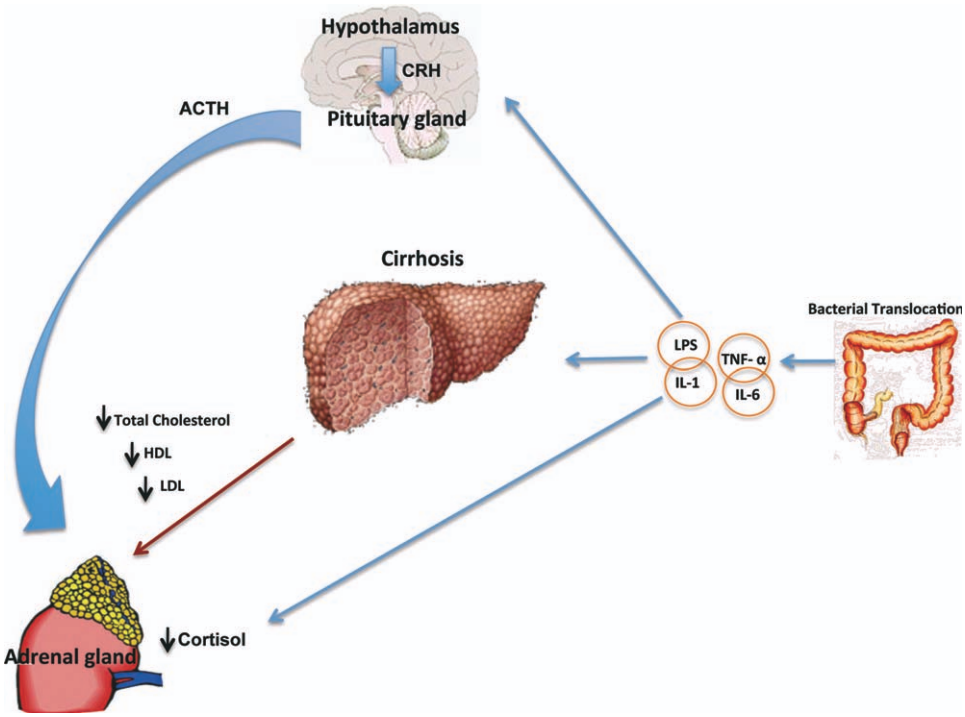

Fig. 1. Possible causes of adrenal dysfunction in liver disease. LPS, lipopolysaccharide.

an essential precursor for steroid biosynthesis in adrenal glands.[38] A decrease in total cholesterol, HDL cholesterol, and low-density lipoprotein (LDL) cholesterol concentrations has been shown in cirrhosis, related to the severity of liver disease.[39] This could lead to lack of substrates and to a progressive exhaustion of adrenal reserve (i.e., "adrenal-exhaustion syndrome").[16] Furthermore, patients with both acute liver disease and CLD have increased levels of circulating endotoxin (e.g., lipopolysaccharide) and proinflammatory cytokines (e.g., tumor necrosis factor alpha [TNF-α], interleukin [IL]-1, and IL-6) that could impair the HPA axis.[40] In particular, TNF-α has been shown to reduce the secretion of ACTH from the pituitary gland.[41]

Systemic inflammation-associated glucocorticoid resistance is characterized by the failure of activated glucocorticoids to down-regulate the transcription of inflammatory cytokines, despite elevated levels of circulating cortisol.[12] It may also contribute to AI in patients with liver disease.

Glucocorticoids have an important role in immunomodulation, supporting many components of inflammatory response to several injuries.[32] Patients with cirrhosis have an increased susceptibility to bacterial infections.[34] This could be partly the result of AI. In critical illness, AI is associated with greater hemodynamic instability and reduced response to vasoactive drugs.[2] Both of these abnormalities could lead to a higher incidence of hemodynamic dysfunction in patients with liver disease and AI (Fig. 2).

Further studies are needed to clarify the clinical importance of HPA dysfunction during liver disease. Such studies should assess the HPA axis with an adequate diagnostic approach and have a prolonged follow-up to assess possible complications or adverse outcomes related to the presence of HPA dysfunction. Last, the effect of corticosteroid supplementation in patients with liver disease and acute decompensation (i.e., bleeding) or critical events (i.e., sepsis and shock) should be assessed prospectively within randomized, clinical trials.

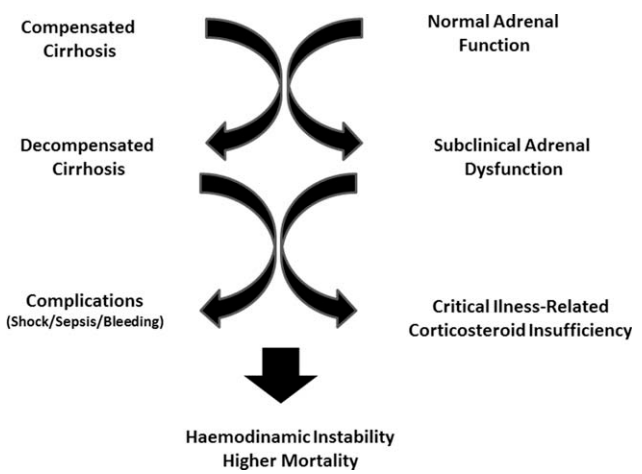

Fig. 2. Clinical relevance of adrenal insufficiency in liver disease.

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