Systematic Review

Systematic Review: Endocrine Abnormalities in Patients with Liver Cirrhosis

Ahad Eshraghian MD•[1], Seyed Alireza Taghavi MD[1,2]

Abstract

Background: Cirrhosis is the end stage of many different forms of acute and chronic liver damages. Interactions between liver and endocrine system is significant, because liver is the main organ of metabolism and catabolism of many proteins.

Aim: In this study, current literature about endocrine abnormalities among patients with liver cirrhosis was reviewed.

Methods: A PubMed search was performed on English literature from January 1990 onward to find human studies reporting endocrine dysfunction in liver cirrhosis. Relevant articles were included and reviewed by two expert reviewers. Data were summarized ant tabulated in separate categories for each endocrine involvement.

Results: Among 944 studies, 36 articles were eligible for review. Growth hormone resistance and low Insulin like growth factor-1 are prevalent in patients with liver cirrhosis with negative impact on prognosis. Thyroid dysfunction is mostly seen in the form of sick euthyroid syndrome. Osteoporosis is also prevalent in cirrhosis but the exact mechanism is not clear. Adrenal insufficiency is a prevalent clinical feature both in compensated and critically ill patients with cirrhosis with negative impact on patients' outcomes.

Conclusion: Disorders of endocrine system is prevalent in cirrhosis. These patients should be checked and treated for these disorders to achieve a stable clinical situation and prepare for liver transplantation.

Key words: Growth hormone, liver cirrhosis, non-alcoholic fatty liver disease, osteoporosis, thyroid disease

Cite this article as: Eshraghian A, Taghavi SA. Systematic Review: Endocrine Abnormalities in Patients with Liver Cirrhosis. *Arch Iran Med*. 2014; **17(10):** 713 – 721.

Introduction

Cirrhosis is the common end stage of acute and chronic liver damages. Nonalcoholic steatohepatis (NASH) is going to become the leading cause of liver cirrhosis among all populations in parallel with the global increase in diabetes, obesity and metabolic syndrome.[1] In industrialized countries chronic hepatitis C and alcoholism are still two leading causes of cirrhosis.[2] Autoimmune hepatitis, metabolic liver disease, Wilson disease and primary billiary cirrhosis are among other causes of liver cirrhosis.

Irrespective of etiology, liver cirrhosis and its complications can affect other body organs and cause a great morbidity and mortality. Portal hypertension is the most important consequence of liver cirrhosis and is the main cause of death among these patients. Bleeding from gastroesophageal varices, ascites, hepatic encephalopathy, coagulopathy, and spontaneous bacterial peritonitis are all complications of cirrhosis that can be potentially lethal. Hepato-renal and hepato-pulmonary syndromes are involvement of kidneys and lungs in the context of liver cirrhosis and are warnings for poor prognosis.[2,3]

Endocrine system is a complex, sophisticated system that involves in many physiological and pathological processes and functions in human body. Liver is thoroughly involved in proteins, cytokines, and interleukins synthesis and destruction. Therefore, abnormal function of endocrine organs is expectable in patients with liver cirrhosis. An alteration in growth hormone (GH) and insulin-like growth factor-1 (IGF-1) secretion pattern has been described in chronic liver disease.[4] According to previous studies, Liver has an important role in metabolism of thyroxin binding globulin and alterations in thyroid hormones.[5] Adrenal insufficiency is also seen either in patients with compensated or decompensated cirrhosis.[6] Male patients with cirrhosis have clinical features of hypogonadism like gynecomastia, loss of libido and infertility while women experience amenorrhea or oligomenorrhea.[7] Disorders of bone metabolism and alterations in serum prolactine level have been also described.[8]

In this study, we reviewed current literature about endocrine abnormalities in patients with liver cirrhosis.

Materials and Methods

Search strategy

The study was conducted using PRISMA (Preferred reporting items for systematic review and meta-analyses) guidelines, flow diagram and checklist.[9] A computerized English language literature search of PubMed was performed in September 2012. Studies that had been published after January 1990 were included to be reviewed. Studies on animal models were excluded. After a preliminary search in MeSH database, we categorized our search to five steps according to endocrine organ. We used terms, "liver cirrhosis" and "thyroid", "liver cirrhosis" and "growth hormone", "liver cirrhosis" and "insulin like growth factor-1 (IGF-1)", "liver cirrhosis" and "adrenal insufficiency", "liver cirrhosis" and "os-

Authors' affiliations: [1]Department of Internal Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. [2]Gatroenterohepatology research center, Shiraz University of Medical Sciences, Shiraz, Iran.
•Corresponding author and reprint: Ahad Eshraghian MD, Department of Internal Medicine, Nemazee Hospital, Shiraz, Iran. P.O. Box: 71345-1744, Shiraz, Iran. Tel: +98-711-6125600 , Fax: +98-711-6276212,
E-mail: Eshraghiana@yahoo.com
Accepted for publication: 23 July 2014

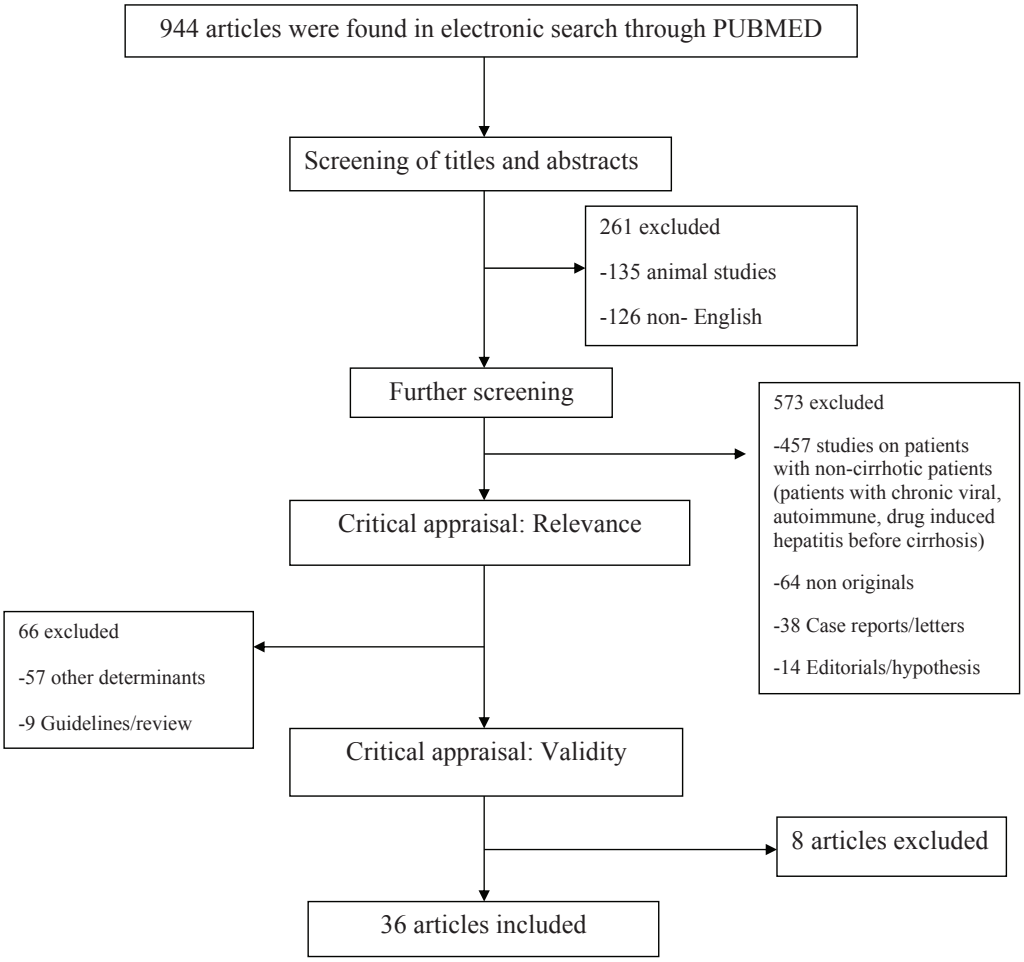

Figure 1. Flow diagram of review.

teoporosis", "liver cirrhosis" and "osteomalacia", "liver cirrhosis" and "hypogonadism", "liver cirrhosis" and "diabetes", and "liver cirrhosis" and hypothalamus/pituitary" as key words in titles and/or abstracts.

Eligibility and critical appraisal of the studies

A large number of references (study titles and abstracts) was reviewed and carefully appraised in this study. All descriptive/analytical cross sectional, and case-control studies, as well as clinical trials with proper methods for assessment of liver cirrhosis and measurement of hormones were included. Editorials, case reports, letters to the editor, hypotheses, studies on animals or cell lines, as well as abstracts from conferences or unpublished reports were excluded. Studies on patients with liver disease other than cirrhosis were excluded. Therefore, studies on patients with chronic viral hepatitis, acute liver failure, hepatocellular carcinoma, and drug-induced hepatitis were also excluded (Figure 1).

Data extraction

Two reviewers abstracted data from full-texts of all relevant articles. Data from these articles reports thyroid hormone abnormalities in cirrhosis, adrenal insufficiency in cirrhosis, as well as the prevalence of osteoporosis in cirrhosis and prognostic value of IGF-1/GH in cirrhosis were extracted and outlined in separate tables.

Results

As a result of our electronic search, 110 studies out of 944 studies were reviewed and appraised for relevance and validity. After exclusion of studies with other determinants, studies that are not representative of our aims, case reports, editorials, finally 36 studies were included and the results were categorized in sub sections. Ten studies reported GH/IGF-1 level in liver cirrhosis and their prognostic significance in these patients.[18–26] These studies showed that GH resistance and low IGF-1 are prevalent in patients with liver cirrhosis with negative impact on prognosis (Table 1). Seven cross-sectional studies were found to investigate thyroid hormone abnormalities in patients with liver cirrhosis (Table 2).[39–44] Nine studies reported the prevalence of osteoporosis in liver cirrhosis (Table 3). Osteoporosis was more prevalent in lumbar area and in patients with primary biliary cirrhosis as underlying cause of liver cirrhosis.[60–68] There were ten studies reporting prevalence of adrenal insufficiency in patients with liver cirrhosis.[73–82] Adrenal insufficiency was a prevalent clinical feature both in compensated and critically ill patients with cirrhosis with negative impact on patients' outcomes (Table 4).

Table 1. Prognostic value of IGF-1/ GH in patients with liver cirrhosis.

Study	Number of patients	Underlying disease	Correlation with liver dysfunction	Pattern of abnormality
Dehghani et al.[18]	45	Viral/metabolic/PFIC PSC/Wilson/BA Cryptogenic	+ +	↓IGF-1 & ↓IGFBP-3
Assy et al.[19]	53	cryptogenic / viral	+	↓ IGF-1
Lorenzo-Zuniga et al.[20]	40	HCV	+	↓ IGF-1
Wu et al.[21]	44	Viral	+ +	↓IGF-1 &2 ↓ IGFBP3
Viyantiadis et al.[22]	40	Viral/PBC/alcoholic	+	↓IGF-1
Donaghy et al.[16]	50	Viral/PBC/PSC/ AIH Metabolic/alcohol	+ +	↓IGF-1 ↓IGFBP-3
Moller et al.[23]	38	NA	_	GHBP
Assy et al.[24]	15	NA	_	IGF-1/GHBP IGFBP-3
Caregaro et al.[25]	64	NA	+	↓IGF-1
Moller et al.[26]	36	Alcoholic	+	↓IGF-1

IGF-1 = insulin like growth factor-1, GH = growth hormone, IGFBP-3 = insulin like growth factor binding protein-3, GHBP = growth hormone binding protein, PFIC = progressive fibrosing intrahepatic cholestasis, BA = biliary atresia, PBC = primary biliary cirrhosis, PSC = primary sclerosing cholangitis, AIH = autoimmune hepatitis, HCV = hepatitis C virus, NA = not available.

Table 2. Thyroid hormone abnormalities in liver cirrhosis.

Study	Number of patients	Underlying disease	Prevalence of TD	Pattern of abnormality
Corpechot[39]	205	PBC	26 (13%)	AITD
Caregaro[40]	75	Alcoholic/viral	23 (30.6%)	↓ T4
Moustafa[41]	59	HCV	NA	↓T3, ↑TSH
Tas[42]	106	Viral/AIH/PBC /Wilson/ Cryptogenic/Alcohol	65 (61.3%)	SUS
El-Kabbany [36]	40	Viral/Metabolic/AIH/ BA/Budd chiary/Wilson	NA	↓FT3
Seehofer[43]	22	Viral/PBC/Alcohol/ Cryptogenic	NA	↓T3, ↓FT3
Silveira[44]	67	PBC	9 (13.4%)	Hypo & hyperthyroidism

PBC= primary biliary cirrhosis, AITD = autoimune thyroid disease, HCV = hepatitis C virus, AIH = autoimmune hepatitis, BA = biliary atresia, SUS = sick euthyroid syndrome, NA = not available.

Table 3. Prevalence of osteoporosis in patients with liver cirrhosis.

Study	Number of patients	Underlying disease	Prevalence of Osteoporosis
Mahmoudi[60]	109	Viral/Alcoholic	11% lumbar 3.6% femur
Loria [61]	35	Alcoholic/viral	14% femur
Guanabens[62]	185	PBC	30.6% lumbar 12.9% femur
Wariaghi[63]	64	Viral/PBC	42.1% lumbar & hip
Guichelaar[64]	360	PBC/PSC	37% lumbar
Sokhi[65]	104	Viral	8.6% lumbar 2.9% femur
Carey[66]	207	Viral/Alcoholic	13.8% lumbar
Ninkovic[67]	243	Mixed	36.6% lumbar &femur
Monegal[68]	58	Mixed	43%

PBC = primary biliray cirrhosis, PSC = primary sclerosing cholangitis.

Table 4. Prevalence and clinical significance of adrenal insufficiency (AI) in liver cirrhosis.

Study	Number of patients	Definition of AI	Prevalence of AI (%)	Relation with severe disease
Triantos et al.[73]	20	**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	No
		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	48	
Risso et al.[74]	85	delta cortisol <250 nmol/L and/or peak cortisol <494 nmol/L after SST	39	Yes
Acevedo et al.[75]	166	delta cortisol <250 nmol/L after SST	26	Yes
Thevenot et al.[76]	125	SST peak cortisol <510 nmol/L	7.2	Yes
Fede et al.[77]	101	**LDSST** A) peak serum cortisol <494 nmol/L B) peak serum cortisol <442 nmol/L C) delta cortisol <250 nmol/L	38 29 60	Yes
Graupera et al.[78]	37	Basal cortisol <414 nmol/L or delta cortisol <250 nmol/L after SST	38	Yes
Avecedo et al.[79]	198	basal cortisol <414 nmol/L and/or delta cortisol <250 nmol/L	26	Yes
Tan et al.[80]	43	**SST** A) peak total cortisol <500 nmol/L 39 B) delta cortisol <250 nmol/L 47 C) peak plasma free cortisol <33 nmol/L	39 47 12	Yes
Galbios et al.[81]	88	**SST** A) basal serum total cortisol <250 nmol/L and/or peak total cortisol<494 nmol/L and/or delta cortisol <250 nmol/L B) basal salivary cortisol <1.8 ng/mL and/or poststimulation values <12.7 ng/mL and/or increase in values <3 ng/mL	33 9	No
Zietz et al.[82]	50	**CRH** A) rise of plasma ACTH <twice the baseline B) peak cortisol value <550 nmol/L or an increase <250 nmol/L	42 58	Yes

SST = short synacthen test, LDSST = low dose short synacthen test, CRH = corticotrophin- releasing hormone test.

Discussion

Growth hormone (GH) and insulin like growth factor-1 (IGF-1)

Liver has a central role in GH/IGF-1 axis, since it is the major source of IGF-1. GH is produced in anterior pituitary gland and stimulates production of IGF-1 in the liver by induction of IGF-1 gene transcription in hepatocytes.[10] IGF-1 has a negative feedback effect on GH production and secretion via local inhibitory action on anterior pituitary gland and inhibitory effect on somatostatin secretion from hypothalamus.[11]

Basal plasma GH level is increased in patients with liver cirrhosis.[12] This may be in part to an increased response to GH releasing hormone in these patients.[13] On the other hand, serum level of IGF-1 is low in cirrhotic patients as a result of diminished response to GH.[14] Therefore, the negative inhibitory feedback effect of IGF-1 is lacked and results in substantial increase in GH level.

Decreased IGF-1 level is secondary to reduced hepatocyte mass, decreased GH receptors in cirrhotic liver, and IGF binding proteins (IGFBP) as blockers of IGF-1 action.[15,16] These alterations in GH/IGF-1 axis have been proposed to be responsible for disorders of lipid and carbohydrate metabolism, insulin resistance and low bone mass in patients with liver cirrhosis.[17]

According to Table 2, several studies have demonstrated the prognostic value of IGF-1 and GH in liver cirrhosis. Almost all of these studies reported that low IGF-1, and IGFBP-3 is associated with more severe diseases. This finding can be attributed to the development of complications of cirrhosis like malnutrition,[27] insulin resistance,[28] osteoporosis,[29] and impaired immune function[30] in low IGF-1 state.

Low serum levels of IGF-1 and IGFBP-3 have also been correlated with development of hepatocellular carcinoma (HCC) in patients with cirrhosis. In a prospective study by Mazziotti, et al., development of HCC was associated with a reduction in serum IGF-1 independent of grade of cirrhosis. They also suggested that follow up of serum IFG-1 may be useful in precocious diagnosis of tumors.[31] Another study has suggested IGFBP-3 as a better predictor of HCC compared to IGF-1in cirrhosis.[32]

Recently a randomized placebo controlled clinical trial showed beneficial effect of IGF-1 administration in increasing albumin level and improvement of energy metabolism in patients with cirrhosis.[33] However, it should be noted that high serum levels of IGF-1 has been reported to be associated with cancer development and this point may limit the clinical utilization of IGF-1 therapy in cirrhotic patients.

Thyroid dysfunction in liver cirrhosis

Several abnormal alterations in thyroid gland have been identified in patients with liver cirrhosis. These are ranged from alterations in thyroid size, morphology and architectural pattern to alterations in thyroid hormone metabolism and regulation. From

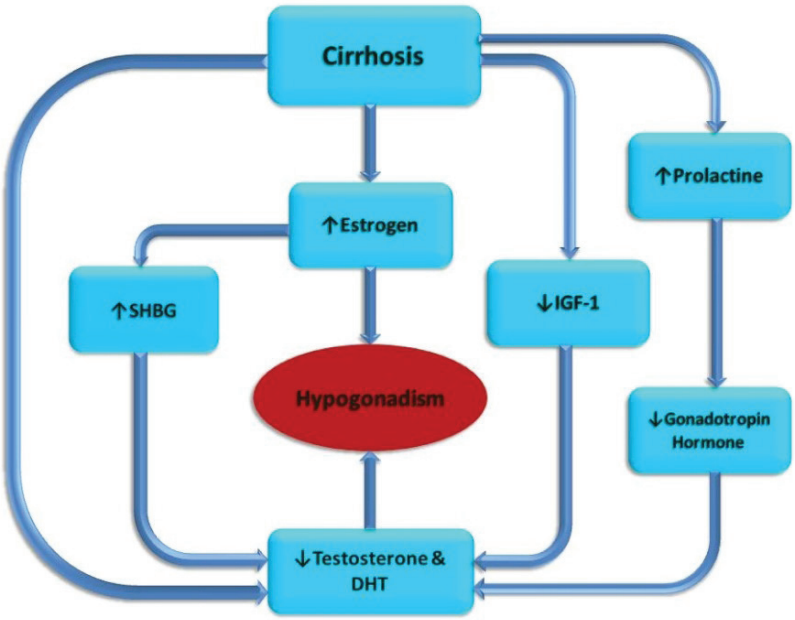

Figure 2. Possible mechanisms of hypogonadism in cirrhosis. IGF-1 = insulin like growth factor-1, DHT = dihydroepiandrosterone, SHBG = sex hormone binding globulin.

morphological aspect, thyroid glandular volume has been reported to be increased up to 17% in patients with cirrhosis compared to non-cirrhotic controls.[34] Thyroid volume is significantly increased in Child C cirrhosis rather than compensated cirrhosis.[35,36] Resistant and pulsatility indices of inferior thyroid artery are increased in cirrhotic patients with respect to healthy individuals.[35,36] Perivascular fibrosis, shorter and thinner follicular diameter and epithelial width were histological features of thyroid gland in cirrhotic patients when compared to non-cirrhotic groups.[37]

Liver is the main organ involved in the peripheral conversion of tetraiodothyronine (T4) to triiodothyroinine (T3) and is the manufacturer of many proteins including thyroid binding proteins.[38] Therefore, dysregulation and dysfunction of thyroid hormones are anticipated in patients with cirrhosis. Studies that reported thyroid hormone abnormalities were outlined in Table 1. The prevalence of thyroid hormone abnormalities ranged from 13 to 61%. A recent study reported that nearly 61% of patients with liver cirrhosis admitted in intensive care units (ICU) had some forms of sick euthyroid syndrome.[42] Although, hypothyroidism was more frequently seen in cirrhosis, hyperthyroidism has been also reported in patients with cirrhosis.[44] Low T3 and low free T3 were the most common pattern of thyroid hormone abnormalities in these studies. This is probably due to reduced deiodinase 1 activity and subsequent impaired hepatic conversion of T4 to T3.[45]

Association between severity of cirrhosis, prognosis and outcomes with thyroid hormones was another topic in several studies. Caregaro, et al., reported that low T4 variants of sick euthyroid syndrome has been associated with decreased short- and long-term survival of patients with liver cirrhosis.[40] Other studies, indicated that low serum T3 is a good index of disease severity in cirrhosis.[46–49] One study demonstrated that significant increase in reverse T3 was accompanied with development of hepatocellular carcinoma in HCV cirrhosis.[50] A retrospective study suggested that a mild controlled hypothyroidism is beneficial in cirrhosis as liver function tests tend to be better in hypothyroid state.[51]

Bone related disorder in cirrhosis

The term hepatic osteodystrophy refers to bone disorders related to chronic liver disease and cirrhosis. The most prevalent bone disease is osteoporosis, however osteomalacia may also be seen (rarely) in cirrhosis.[52] The pathiophysiological basis of osteoporosis in cirrhosis is poorly understood but several mechanisms are proposed. Some risk factors of osteoporosis including malnutrition, hypogonadism, alcohol consumption and use of corticosteroid are seen in cirrhosis. Patients with primary biliary cirrhosis are mostly postmenopausal women that predispose to osteoporosis.

The role of IGF-1 has been proposed in bone metabolism and maintenance of bone mass.[53] Therefore, reduced levels of IGF-1 in cirrhosis may contribute to reduced bone mass and osteoporosis. George, et al., showed that lower serum levels of IGF-1 were associated with low bone mineral density in patients with cirrhosis.[54] Osteoprotegerin (OPG) is a member of tumor necrosis factor receptor superfamily that is secreted from osteoblasts and has an inhibitory effect on osteoclast differentiation.[55] Recent studies in patients with cirrhosis have illustrated the protective effect of OPG not only in bone loss[56] but also in progression of liver disease.[57] However, current studies have provided conflicting results and the precise role of OPG remained to be clarify in future studies. The receptor activator of NF kappa beta (RANK) on osteoblasts and receptor activator of NF kappa beta ligand (RANKL) on osteoclasts are involved in bone resorption.[58] Low serum level of RANKL has been reported in patients with PBC[59] but the exact role of RANK/RANKL in pathophysiology of bone disease in cirrhosis is not clear. Prevalence of osteoporosis has been reported in several studies (Table 3). In these studies osteoporosis was defined as T-score <-2.5. As reported in these studies, osteoporosis is more prevalent in lumbar spine compared to femoral neck among patients with liver cirrhosis. The prevalence of osteopenia (-2.5< T-score <-1) is even higher than osteoporosis in these patients.

Adrenal insufficiency in liver cirrhosis

Adrenal insufficiency is a common feature in critically ill patients. Adrenal insufficiency has been reported both in patients with compensated and stable cirrhosis as well as in cirrhotic patients in septic shock.[69] Sometimes the adrenal disorder in the context of liver disease is called hepatoadrenal syndrome,[70] although the mechanisms of hypothalamus-pituitary-adrenal (HPA) axis dysfunction are not clear in liver disease. Low level of cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) are established laboratory findings in cirrhosis.[71] Cholesterol is a precursor for adrenal gland to produce steroids. When cholesterol level is decreased the adrenal gland will no longer have enough substrate to produce hormones. On the other hand, tumor pro-inflammatory cytokines especially necrosis factor alpha (TNF-α), with increased level in cirrhosis, has been reported to reduce adreno-cortico-tropic-hormone (ACTH) secretion from pituitary gland.[72] Table 4 summarizes prevalence and clinical significance of adrenal insufficiency in patients with liver cirrhosis which are not critically ill. Table 4 demonstrates the prevalence of adrenal insufficiency ranged from 7.2% to 60% in different studies. This wide variability is due to different lab test and criteria for definition of adrenal insufficiency. Nearly all of the studies showed bad prognosis in cirrhotic patients with adrenal insufficiency.

Hypothalamus-pituitary-gonadal axis in liver cirrhosis

Hypogonadism is a frequent clinical feature in patients with liver cirrhosis. These patients have gynecomastia, decreased libido, signs of feminization, testicular atrophy and low testosterone level, as well as infertility and reduced spermatogenesis.[83] These features are more severe in patients with higher Child Pugh score.[84] Erectile dysfunction and reduced sexual activity are seen in patients with more severe cirrhosis. The severity of cirrhosis is assessed using the model for end-stage liver disease (MELD).[85] Above mentioned abnormalities are more prominent in patients with alcoholic cirrhosis due to direct effect of ethanol on testis.[86] Several hormonal abnormalities are responsible for these clinical alterations. Estrogen/androgen ratio has been increased in cirrhosis while there is a reduction in serum testosterone and dihydroepiandrosterone level.[87] A mild elevation in serum estradiol has been also showed in several studies.[87] Hyperprolactinemia is present in patients with cirrhosis and may involve in hypogonadism by an inhibitory effect on gonadotropin.[88] Sex binding hormone globulin (SHBG) is a protein, which is produced by the liver and binds to testosterone with high affinity. Estrogens have a stimulatory effect on production of SHBG, while androgens inhibit its production and secretion. Conditions with excess estrogen accompany with increased production of SHBG and subsequent reduction in free testosterone and dihydroepiandrosterone.[89] This may also participate in feminized features in cirrhosis. Finally, we should remind the role of IGF-1 in hypogonadism. IGF-1 stimulates testosterone production and spermatogenesis.[90] Therefore, IGF-1 deficiency as seen in cirrhosis can result in hypogonadism (Figure 2). Female patients with cirrhosis suffer from amenorrhea, oligomenorrhea, or irregular episodes of metrorrhagia.[85] These alterations are generally normalized after liver transplantation.

Metabolic syndrome and insulin resistance in liver disease

Metabolic syndrome is a constellation of metabolic abnormalities including diabetes, hyperlipidemia, central obesity and hypertension.[91] The high incidence of diabetes in patients with liver cirrhosis has been known from years ago.[92] On the other hand patients with diabetes are more susceptible to chronic liver disease and HCC.[93] Metabolic syndrome and diabetes are not only prevalent among patients with chronic liver diseases but also can occur after liver transplantation.[94–97] The terms non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are hepatic manifestations of insulin resistance and metabolic syndrome.[98] In patients with NAFLD, the incidence of type II diabetes is increased independent of insulin resistance and obesity.[99] Based on these findings, screening of patients with NAFLD for type II diabetes have been suggested by some authors.[100]

Insulin resistance (IR) is central to pathogenesis of NAFLD. Accumulation of triglycerides and steatosis as consequence of systemic IR is the first hit in "two hit hypothesis" described by Day, et al.[101] Oxidative stress secondary to long term accumulation of triglycerides is the second hit in this theory. The "multiple hit hypothesis" suggests multiple parallel phenomenons are acting together in pathogenesis of NAFLD and subsequent liver fibrosis.[102] Irrespective of these two main hypotheses, IR is the main underlying cause for NAFLD and NASH.

Thyroid hormone abnormalities have been shown in patients with NAFLD.[103,104] We have recently shown that a pattern of sick euthyroid syndrome is prevalent in patients with NAFLD and the diagnosis of NAFLD is significantly higher in those with lower TSH.[105] Our observation have been recently confirmed in an animal model of NAFLD.[106]

Endocrine abnormalities in hereditary hemochromatosis

Hereditary hemochromatosis (HH) is an autosomal recessive disorder caused by mutations in HFE gene resulting in excessive absorption of iron and accumulation of iron in paranchymal cells of different organs as well as subsequent organ dysfunction.[107] This leads to liver cirrhosis, diabetes, cardiomyopathy, hypogonadism and arthropathy. The prevalence of diabetes in patients with HH is usually between 20% to 50%.[108] Both insulin deficiency and insulin resistance are contributing factors in diabetes occurred in HH.[109] Hepatic iron overload may firstly cause insulin resistant state and then b-cell destruction promotes development of C-peptide negative diabetes requiring insulin therapy.[110] It is interesting that reduction of iron overload by phlebotomy, iron chelators or low iron diets has had protective role against diabetes in animal models by increasing insulin secretion and improvement of insulin sensitivity.[111,112]

Nearly half of patients with HH have hypogonadism. The main pathogenesis is hypogonadotropic hypogonadsim; however, deposition of iron within gonads may cause secondary hypognadism. These patients may present with infertility, impotence with low testosterone and azoospermia.[113]

Here in, we reviewed available evidences about endocrine system abnormalities in patients with liver cirrhosis. Endocrine hormones are proteins and steroids that are produced and secreted by different endocrine glands. Liver is an organ, which is totally involved in metabolism and catabolism of many hormones in the body and has a close interaction with endocrine system. Growth hormone resistance with low serum IGF-1 is prevalent in liver cirrhosis that may result in insulin resistance, osteoporosis and hypogonadism. Liver cirrhosis can affect thyroid mainly in forms of sick euthyroid syndrome or hypothyroidism, although most of the patients are clinically euthyroid. Adrenal insufficiency, osteoporosis and hypogonadism are other clinical abnormalities of endocrine system in liver cirrhosis.

Declaration of funding and personal interest

None.

Grant support

Nothing

References

1. Starr SP, Raines D. Cirrhosis: diagnosis, management, and prevention. *Am Fam Physician*. 2011; **84:** 1353 – 1359.
2. Taghavi SA, Eshraghian A, Hamidpour L, Moshfe MJ. Endoscopic cyanoacrylate injection for the treatment of bleeding gastric varices: the first Iranian series. *Arch Iran Med*. 2012; **15:** 157 – 161.
3. Eshraghian A, Kamyab AA, Yoon SK. Pharmacological treatment for hepatopulmonary syndrome. *Biomed Res Int*. 2013; **2013:** 670139.
4. De Palo EF, Bassanello M, Lancerin F, Spinella P, Gatti R, D'Amico D, et al. GH/IGF system, cirrhosis and liver transplantation. *Clin Chim Acta*. 2001; **310:** 31 – 37.
5. Borzio M, Caldara R, Borzio F, Piepoli V, Rampini P, Ferrari C. Thyroid function tests in chronic liver disease: evidence for multiple abnormalities despite clinical euthyroidism. *Gut*. 1983; **24:** 631 – 636.
6. McDonald JA, Handelsman DJ, Dilworth P, Conway AJ, McCaughan GW. Hypothalamic-pituitary adrenal function in end-stage non-alcoholic liver disease. *J Gastroenterol Hepatol*. 1993; **8:** 247 – 253.
7. Sorrell JH, Brown JR. Sexual functioning in patients with end-stage liver disease before and after transplantation. *Liver Transpl*. 2006; **12:** 1473 – 1477.
8. Collier J. Bone disorders in chronic liver disease. *Hepatology*. 2007; **46:** 1271 – 1278.
9. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Med*. 2009; **6:** e1000100.
10. Daughaday WH, Rotwein P. Insulin-like growth factors I and II. Peptide, messenger ribonucleic acid and gene structures, serum, and tissue concentrations. *Endocr Rev*. 1989; **10:** 68 – 91.
11. Clifford J, Rosen MP. Circulating IGF-I: new perspectives for a new century. *Trends Endocrinol Metab*. 1999; **10:** 136 – 141.
12. Shankar TP, Fredi JL, Himmelstein S, Solomon SS, Duckworth WC. Elevated growth hormone levels and insulin resistance in patients with cirrhosis of the liver. *Am J Med Sci*. 1986; **291:** 248 – 254.
13. Salerno F, Locatelli V, Muller EE. Growth hormone hyper responsiveness to growth hormone-releasing hormone in patients with severe liver cirrhosis. *Clin Endocrinol*. 1987; **27:** 183 – 190.
14. Muggeo M, Tiengo A, Fedele D, Crepaldi G. Altered control of growth hormone secretion in patients with cirrhosis of the liver. *Arch Intern Med*. 1979; **139:** 1157 – 1160.
15. Shen XY, Holt RI, Miell JP, Justice S, Portmann B, Postel-Vinay MC, et al. Cirrhotic liver expresses low levels of the full-length and truncated growth hormone receptors. *J Clin Endocrinol Metab*. 1998; **83:** 2532 – 2538.
16. Donaghy AJ, Delhanty PJ, Ho KK, Williams R, Baxter RC. Regulation of the growth hormone receptor/binding protein, insulin-like growth factor ternary complex system in human cirrhosis. *J Hepatol*. 2002; **36:** 751– 758.
17. Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. *Endocr Rev*. 1995; **16:** 3 – 34.
18. Dehghani SM, Karamifar H, Hamzavi SS, Haghighat M, Malek-Hosseini SA. Serum insulin like growth factor-1 and its binding protein-3 levels in children with cirrhosis waiting for a liver transplant. *Exp Clin Transplant*. 2012; **10:** 252 – 257.
19. Assy N, Pruzansky Y, Gaitini D, Shen Orr Z, Hochberg Z, Baruch Y. Growth hormone-stimulated IGF-1 generation in cirrhosis reflects hepatocellular dysfunction. *J Hepatol*. 2008; **49:** 34 – 42.
20. Lorenzo-Zúñiga V, Bartolí R, Masnou H, Montoliu S, Morillas RM, Planas R. Serum concentrations of insulin-like growth factor-I (igf-I) as a marker of liver fibrosis in patients with chronic hepatitis C. *Dig Dis Sci*. 2007; **52:** 3245 – 3250.
21. Wu YL, Ye J, Zhang S, Zhong J, Xi RP. Clinical significance of serum IGF-I, IGF-II and IGFBP-3 in liver cirrhosis. *World J Gastroenterol*. 2004; **10:** 2740 – 2743.
22. Vyzantiadis T, Theodoridou S, Giouleme O, Harsoulis P, Evgenidis N, Vyzantiadis A. Serum concentrations of insulin-like growth factor-I (IGF-I) in patients with liver cirrhosis. *Hepatogastroenterology*. 2003; **50:** 814 – 816.
23. Møller S, Fisker S, Becker U, Henriksen JH. A comparison of circulating and regional growth hormone-binding protein in cirrhosis. *Metabolism*. 2001; **50:** 1340 – 1345.
24. Assy N, Hochberg Z, Enat R, Baruch Y. Prognostic value of generation of growth hormone-stimulated insulin-like growth factor-I (IGF-I) and its binding protein-3 in patients with compensated and decompensated liver cirrhosis. *Dig Dis Sci*. 1998; **43:** 1317 – 1321.
25. Caregaro L, Alberino F, Amodio P, Merkel C, Angeli P, Plebani M, et al. Nutritional and prognostic significance of insulin-like growth factor 1 in patients with liver cirrhosis. *Nutrition*. 1997; **13:** 185 – 190.
26. Møller S, Grønbaek M, Main K, Becker U, Skakkebaek NE. Urinary growth hormone (U-GH) excretion and serum insulin-like growth factor 1 (IGF-1) in patients with alcoholic cirrhosis. *J Hepatol*. 1993; **17:** 315 – 320.
27. Thissen JP, Ketelslegers JM, Underwood LE. Nutritional regulation of the insulin-like growth factors. *Endocr Rev*. 1994; **15:** 80 – 101.
28. Shmueli E, Miell JP, Stewart M, Alberti KG, Record CO. High insulin-like growth factor binding protein 1 levels in cirrhosis: link with insulin resistance. *Hepatology*. 1996; **24:** 127 – 133.
29. Gallego-Rojo FJ, Gonzalez-Calvin JL, Munoz-Torres M, Mundi JL, Fernandez-Perez R, Rodrigo-Moreno D. Bone mineral density, serum insulin-like growth factor I, and bone turnover markers in viral cirrhosis. *Hepatology*. 1998; **28:** 695 – 699.
30. Mendenhall CL, Roselle GA, Gartside P, Grossman CJ. Effects of recombinant human insulin-like growth factor-1 and recombinant human growth hormone on anabolism and immunity in calorie restricted alcoholic rats. *Alcohol Clin Exp Res*. 1997; **21:** 1 – 10.
31. Mazziotti G, Sorvillo F, Morisco F, Carbone A, Rotondi M, Stornaiuolo G, et al. Serum insulin-like growth factor I evaluation as a useful tool for predicting the risk of developing hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis: a prospective study. *Cancer*. 2002; **95:** 2539 – 2545.
32. Aleem E, Elshayeb A, Elhabachi N, Mansour AR, Gowily A, Hela A. Serum IGFBP-3 is a more effective predictor than IGF-1 and IGF-2 for the development of hepatocellular carcinoma in patients with chronic HCV infection. *Oncol Lett*. 2012; **3:** 704 – 712.
33. Conchillo M, de Knegt RJ, Payeras M, Quiroga J, Sangro B, Herrero JI, et al. Insulin-like growth factor I (IGF-I) replacement therapy increases albumin concentration in liver cirrhosis: results of a pilot randomized controlled clinical trial. *J Hepatol*. 2005; **43:** 630 – 636.
34. Bianchi GP, Zoli M, Marchesini G, Volta U, Vecchi F, Iervese T, et al. Thyroid gland size and function in patients with cirrhosis of the liver. *Liver*. 1991; **11:** 71 – 77.
35. Spadaro L, Bolognesi M, Pierobon A, Bombonato G, Gatta A, Sacerdoti D. Alterations in thyroid Doppler arterial resistance indices, volume and hormones in cirrhosis: relationships with splanchnic haemodynamics. *Ultrasound Med Biol*. 2004; **30:** 19 – 25.
36. El-Kabbany ZA, Hamza RT, Abd El Hakim AS, Tawfik LM. Thyroid and hepatic haemodynamic alterations among Egyptian children with liver cirrhosis. *ISRN Gastroenterol*. 2012; **2012:** 595734.
37. Gemma R, Miura K, Mikami T, Natsume H, Nishiyama K, Nakamura H. Histological changes of thyroid tissues in patients with liver cirrhosis. *Endocr J*. 2001; **48:** 535 – 542.
38. Huang MJ, Liaw YF. Clinical associations between thyroid and liver diseases. *J Gastroenterol Hepatol*. 1995; **10:** 344 – 350.
39. Corpechot C, Chrétien Y, Chazouillères O, Poupon R. Demographic, lifestyle, medical and familial factors associated with primary biliary cirrhosis. *J Hepatol*. 2010; **53:** 162 – 169.
40. Caregaro L, Alberino F, Amodio P, Merkel C, Angeli P, Plebani M, et al. Nutritional and prognostic significance of serum hypothyroxinemia in hospitalized patients with liver cirrhosis. *J Hepatol*. 1998; **28:** 115 – 121.
41. Moustafa AH, Ali EM, Mohamed TM, Abdou HI. Oxidative stress and thyroid hormones in patients with liver diseases. *Eur J Intern Med*. 2009; **20:** 703 – 708.
42. Taş A, Köklü S, Beyazit Y, Kurt M, Sayilir A, Yeşil Y, et al. Thyroid hormone levels predict mortality in intensive care patients with cirrhosis. *Am J Med Sci*. 2012; **344:** 175 – 179.
43. Seehofer D, Steinmueller T, Graef KJ, Rayes N, Wiegand W, Tullius SG, et al. Pituitary function test and endocrine status in patient with cirrhosis of the liver before and after hepatic transplantation. *Ann Transplant*. 2002; **7:** 32 – 37.

44. Silveira MG, Mendes FD, Diehl NN, Enders FT, Lindor KD. Thyroid dysfunction in primary biliary cirrhosis, primary sclerosing cholangitis and non-alcoholic fatty liver disease. *Liver Int*. 2009; **29:** 1094 – 1100.
45. Huang MJ, Liaw YF. Clinical associations between thyroid and liver diseases. *J Gastroenterol Hepatol*. 1995; **10:** 344 – 350.
46. Rodríguez-Torres M, Ríos-Bedoya CF, Ortiz-Lasanta G, Marxuach-Cuétara AM, Jiménez-Rivera J. Thyroid dysfunction (TD) among chronic hepatitis C patients with mild and severe hepatic fibrosis. *Ann Hepatol*. 2008; **7:** 72 – 77.
47. Mansour-Ghanaei F, Mehrdad M, Mortazavi S, Joukar F, Khak M, Atrkar-Roushan Z. Decreased serum total T3 level in hepatitis B and C related cirrhosis by severity of liver damage. *Ann Hepatol*. 2012; **11:** 667 – 671.
48. Kayacetin E, Kisakol G, Kaya A. Low serum total thyroxine and free triiodothyronine in patients with hepatic encephalopathy due to non-alcoholic cirrhosis. *Swiss Med Wkly*. 2003; **133:** 210 – 213.
49. Güven K, Kelestimur F, Yücesoy M. Thyroid function tests in non-alcoholic cirrhotic patients with hepatic encephalopathy. *Eur J Med*. 1993; **2:** 83 – 85.
50. Sorvillo F, Mazziotti G, Carbone A, Morisco F, Cioffi M, Rotondi M, et al. Increased serum reverse triiodothyronine levels at diagnosis of hepatocellular carcinoma in patients with compensated HCV-related liver cirrhosis. *Clin Endocrinol (Oxf)*. 2003; **58:** 207 – 212.
51. Oren R, Brill S, Dotan I, Halpern Z. Liver function in cirrhotic patients in the euthyroid versus the hypothyroid state. *J Clin Gastroenterol*. 1998; **27:** 339 – 341.
52. AGA Clinical Practice Committee. AGA technical review on osteoporosisin hepatic disorders. *Gastroenterology*. 2003; **125:** 941 – 966.
53. Chen J, Yuan K, Mao X, Miano JM, Wu H, Chen Y. Serum response factor regulates bone formation via IGF-1 and Runx2 signals. *J Bone Miner Res*. 2012; **27:** 1659 – 1668.
54. George J, Ganesh HK, Acharya S, Bandgar TR, Shivane V, Karvat A, et al. Bone mineral density and disorders of mineral metabolism in chronic liver disease. *World J Gastroenterol*. 2009; **15:** 3516 – 3522.
55. Moschen AR, Kaser A, Stadlmann S. The RANKL/OPG system and bone mineral density in patients with chronic liver disease. *J Hepatol*. 2005; **43:** 973 – 983.
56. González-Calvin JL, Mundi JL, Casado-Caballero FJ, Abadia AC, MartinIbañez JJ. Bone mineral density and serum levels of soluble tumor necrosis factors, estradiol, and osteoprotegerin in postmenopausal women with cirrhosis after viral hepatitis. *J Clin Endocrinol Metab*. 2009; **94:** 4844 – 4850.
57. Nanda KS, Brady JJ, Murray BF, Sullivan O, Fearon U, McKenna MJ, et al. Elevated circulating osteoprotegerin and reduced matrix-metalloprotease-9 in post-menopausal women with chronic Hepatitis C virus infection. *Cytokine*. 2012; **60:** 328 – 333.
58. Boyle WJ, Scott-Simonet W, Lacey DL. Osteoclast differentiation and activation. *Nature*. 2003; **423:** 337 – 342.
59. Szalay F, Hegedus D, Lakatos PL, Tornai I, Bajnok E, Dunkel K, et al. High serum osteoprotegerin and low RANKL in primary biliary cirrhosis. *J Hepatol*. 2003; **38:** 395 – 400.
60. Mahmoudi A, Sellier N, Reboul-Marty J, Chalès G, Lalatonne Y, Bourcier V, et al. Bone mineral density assessed by dual-energy X-ray absorptiometry in patients with viral or alcoholic compensated cirrhosis. A prospective study. *Clin Res Hepatol Gastroenterol*. 2011; **35:** 731 – 737.
61. Loria I, Albanese C, Giusto M, Galtieri PA, Giannelli V, Lucidi C, et al. Bone disorders in patients with chronic liver disease awaiting liver transplantation. *Transplant Proc*. 2010; **42:** 1191 – 1193.
62. Guañabens N, Cerdá D, Monegal, A Pons F, Caballería L, Peris P, et al. Low bone mass and severity of cholestasis affect fracture risk in patients with primary biliary cirrhosis. *Gastroenterology*. 2010; **138:** 2348 – 2356.
63. Wariaghli G, Mounach A, Achemlal L, Benbaghdadi I, Aouragh A, Bezza A, et al. Osteoporosis in chronic liver disease: a case-control study. *Rheumatol Int*. 2010; **30:** 893 – 899.
64. Guichelaar M, Schmoll J, Malinchoc M, Hay EJ. Fractures and avascular necrosis before and after orthotopic liver transplantation: long-term follow-up and predictive factors. *Hepatology*. 2007; **46:** 1198 – 1207.
65. Sokhi RP, Anantharaju A, Kondaveeti R, Creech SD, Islam KK, Van Thiel DH. Bone mineral density among cirrhotic patients awaiting liver transplantation. *Liver Transpl*. 2004; **10:** 648 – 653.
66. Carey EJ, Balan V, Kremers WK, Hay JE. Osteopaenia and osteoporosis in patients with end-stage liver disease caused by hepatitis C and alcoholic liver disease: not just a cholestatic problem. *Liver Transpl*. 2003; **9:** 1166 – 1173.
67. Ninkovic M, Skingle SJ, Bearcroft PWP, Bishop N, Alexander GJM, Compston JE. Incidence of vertebral fracture in the first three months following orthotopic liver transplantation. *Eur J Gastroenterol Hepatol*. 2000; **12:** 931 – 935.
68. Monegal A, Navasa M, Guanabens N, Peris P, Pons F, Martinez de Osaba MJ, et al. Osteoporosis and bone mineral metabolism disorders in cirrhotic patients referred for orthotopic liver transplantation. *Calcif Tissue Int*. 1997; **60:** 148 – 154.
69. Fernandez J, Escorsell A, Zabalza M, Felipe V, Navasa M, Mas A, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: Effect of treatment with hydrocortisone on survival. *Hepatology*. 2006; **44:** 1288 – 1295.
70. Marik PE, Gayowski T, Starzl TE. Hepatic Cortisol Research and Adrenal Pathophysiology Study Group. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. *Crit Care Med*. 2005; **33:** 1254 – 1259.
71. Cicognani C, Malavolti M, Morselli-Labate AM, Zamboni L, Sama C, Barbara L. Serum lipid and lipoprotein patterns in patients with liver cirrhosis and chronic active hepatitis. *Arch Intern Med*. 1997; **157:** 792 – 796.
72. Gaillard RC, Turnill D, Sappino P, Muller AF. Tumor necrosis factor alpha inhibits the hormonal response of the pituitary gland to hypothalamic releasing factors. *Endocrinology*. 1990; **127:** 101 – 106.
73. Triantos C, Marziqie M, Fede G, Michalaki M, Giannakopoulou D, Thomopoulos K, et al. Critical illness related corticosteroid insufficiency(CIRCI) in patients with cirrhosis and variceal bleeding. *Clin Gastroenterol Hepatol*. 2011; **9:** 595 – 601.
74. Risso A, Alessandria C, Elia C, Mezzabotta L, Andrealli A, Spandre M, et al. Adrenal dysfunction in nonseptic cirrhotic patients with ascites: impact on survival [Abstract]. *Digest Liver Dis*. 2011; **43(suppl 2):** S74 – S75.
75. Acevedo J, Fernandez J, Castro M, Roca D, Gine`s P, Arroyo V. Impact of relative adrenal insufficiency on circulatory function and mortality in advanced cirrhosis. *J Hepatol*. 2011; **54:** S61.
76. Thevenot T, Borot S, Remy-Martin A, Sapin R, Cervoni JP, Richou C, et al. Assessment of adrenal function in cirrhotic patients using concentration of serum-free and salivary cortisol. *Liver Int*. 2011; **31:** 425 – 433.
77. Fede G, Spadaro L, Tomaselli T, Privitera G, Piro S, Rabuazzo AM, et al. Assessment of adrenocortical reserve in stable patients with cirrhosis. *J Hepatol*. 2011; **54:** 243 – 250.
78. Graupera I, Hernandez-Gea V, Rodriguez, Colomo A, Poca M, Llao J, et al. Incidence and prognostic significance of relative adrenal insufficiency in cirrhotic patients with severe variceal bleeding [Abstract]. *Hepatology*. 2010; **52:** 267A.
79. Acevedo J, Fernandez J, Castro M, Roca D, Gine`s P, Arroyo V. Prognostic value of relative adrenal insufficiency in decompensated cirrhosis. *J Hepatol*. 2010; **52:** S59.
80. Tan T, Chang L, Woodward A, McWhinney B, Galligan J, Macdonald GA, et al. Characterising adrenal function using directly measured plasma free cortisol in stable severe liver disease. *J Hepatol*. 2010; **53:** 841 – 848.
81. Galbois A, Rudler M, Massard J, Fulla Y, Bennani A, Bonnefont-Rousselot D, et al. Assessment of adrenal function in cirrhotic patients: salivary cortisol should be preferred. *J Hepatol*. 2010; **52:** 839 – 845.
82. Zietz B, Lock G, Plach B, Drobnik W, Grossmann J, Schölmerich J, et al. Dysfunction of the hypothalamic-pituitary-glandular axes and relation to Child-Pugh classification in male patients with alcoholic and virus-related cirrhosis. *Eur J Gastroenterol Hepatol*. 2003; **15:** 495 – 501.
83. Karagiannis A, Harsoulis F. Gonadal dysfunction in systemic diseases. *Eur J Endocrinol*. 2005; **152:** 501.
84. van Thiel DH, Gavaler JS, Spero JA, Egler KM, Wright C, Sanghvi AT, et al. Patterns of hypothalamic pituitary gonadal dysfunction in men with liver disease due to differing etiologies. *Hepatology*. 1981; **1:** 39.
85. Sorrell JH, Brown JR. Sexual functioning in patients with end-stage liver disease before and after transplantation. *Liver Transpl*. 2006; **12:** 1473.
86. Frias J, Torres JM, Miranda MT, Ruiz E, Ortega M. Effects of acute alcohol intoxication on pituitary-gonadal axis hormones, pituitary-adrenal axis hormones, beta-endorphin and prolactin in human adults of both sexes. *Alcohol Alcohol.* 2002; **37:** 169 – 173.

87. Bannister P, Oakes J, Sheridan P, Losowsky MS. Sex hormone changes in chronic liver disease: A matched study of alcoholic versus non-alcoholic liver disease. *Q J Med.* 1987; **63:** 305.
88. Simon-Holtorf J, Mönig H, Klomp HJ, Reinecke-Lüthge A, Fölsch UR, Kloehn S. Expression and distribution of prolactin receptor in normal, fibrotic, and cirrhotic human liver. *Exp Clin Endocrinol Diabetes*. 2006; **114:** 584 – 589.
89. Loukovaara M, Carson M, Adlercrentz H. Regulation of production and secretion of sex hormone-binding globulin in HepG2 cell cultures by hormones and growth factors. *J Clin Endocrinol Metab*. 1995; **80:** 160 – 164.
90. Tajima Y, Watanabe D, Koshimizu U, Matsuzawa T, Nishimune Y. Insulin-like growth factor-I and transforming growth factor-alpha stimulate differentiation of type A spermatogonia in organ culture of adult mouse cryptorchid testes. *Int J Androl.* 1995; **18:** 8 – 12.
91. Eshraghian A. Metabolic syndrome after liver transplantation: is there a role for infections? *Nutrition*. 2012; **28:** 825 – 827.
92. Perseghin G, Mazzaferro V, Sereni LP, Regalia E, Benedini S, Bazzigaluppi E, et al. Contribution of reduced insulin sensitivity and secretion to the pathogenesis of hepatogenous diabetes: effect of liver transplantation. *Hepatology.* 2000; **31:** 694 – 703.
93. Trombetta M, Spiazzi G, Zoppini G, Muggeo M. Review article: type 2 diabetes and chronic liver disease in the Verona diabetes study. *Aliment Pharmacol Ther*. 2005; **22(Suppl 2):** 24 – 27.
94. Dehghani SM, Taghavi SA, Eshraghian A,Gholami S, Imanieh MH, Bordbar MR, et al. Hyperlipidemia in Iranian liver transplant recipients: prevalence and risk factors. *J Gastroenterol*. 2007; **42:** 769 – 774.
95. Lankarani KB, Eshraghian A, Nikeghbalian S, Janghorban P, Malek-Hosseini SA. New onset diabetes and impaired fasting glucose after liver transplant: risk analysis and the impact of tacrolimus dose. *Exp Clin Transplant*. 2014; **12:** 46 – 51.
96. Eshraghian A. New onset diabetes after transplantation: a type 1.5 diabetes or latent autoimmune diabetes of adults? *J Hepatol*. 2013; **58:** 1059 – 1060.
97. Dehghani SM, Nikeghbalian S, Eshraghian A, Haghighat M, Imanieh MH, Bahador A, et al. New-onset diabetes mellitus presenting with diabetic ketoacidosis after pediatric liver transplantation. *Pediatr Transplant*. 2009; **13:** 536 – 539.
98. Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fattyliver disease: the Dionysos Nutrition and Liver Study. *Hepatology*. 2005; **42:** 44 – 52.
99. Sung KC, Jeong WS, Wild SH, Byrne CD. Combined influence of insulin resistance, overweight / obesity, and fatty liver as risk factors for Type 2 diabetes. *Diabetes Care*. 2012; **35:** 717 – 722.
100. Gastaldelli A, Kozakova M, Hojlund K, Flyvbjerg A, Favuzzi A, Mitrakou A, et al. Fatty liver is associated with insulin resistance, risk of coronary heart disease, and early atherosclerosis in a large European population. *Hepatology*. 2009; **49:** 1537 – 1544.
101. Day CP, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology*. 1998; **114:** 842 – 845.
102. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholicfatty liver disease: the multiple parallel hitshypothesis. *Hepatology*. 2010; **52:** 1836 – 1846.
103. Eshraghian A, Hamidian Jahromi A. Nonalcoholic fatty liver disease and thyroid dysfunction: a systematic review. *World J Gastroenterol*. 2014; **20:** 8102 – 8109.
104. Huang YY, Gusdon AM, Qu S. Cross-talk between the thyroid and liver: a new target for nonalcoholic fatty liver disease treatment. *World J Gastroenterol*. 2013; **19:** 8238 – 8246
105. Eshraghian A, Dabbaghmanesh MH, Eshraghian H, Fattahi MR, Omrani GR. Nonalcoholic fatty liver disease in a cluster of Iranian population: thyroid status and metabolic risk factors. *Arch Iran Med*. 2013; **16:** 584 – 589.
106. Dullaart RP, van den Berg EH, van der Klauw MM, Blokzijl H. Low normal thyroid function attenuates serum alanine aminotransferase elevations in the context of metabolic syndrome and insulin resistance in white people. *Clin Biochem*. 2014. pii: S0009-9120(14)00185-4. doi: 10.1016/j.clinbiochem.2014.04.016. [Epub ahead of print]
107. Pietrangelo A. Hereditary hemochromatosis: pathogenesis, diagnosis, and treatment. *Gastroenterology*. 2010; **139:** 393 – 408, 408.e1-2.
108. Hramiak IM, Finegood DT, Adams PC. Factors affecting glucose tolerance in hereditary hemochromatosis. *Clin Invest Med*. 1997; **20:** 110–118.
109. Mendler MH, Turlin B, Moirand R, Jouanolle AM, Sapey T, Guyader D, et al. Insulin resistance-associated hepatic iron overload. *Gastroenterology*. 1999; **117:** 1155–1163.
110. Sampaio AF, Silva M, Dornas WC, Costa DC, Silva ME, Dos Santos RC, et al. Iron toxicity mediated by oxidative stress enhances tissue damage in an animal model of diabetes. *Biometals*. 2014; **27:** 349 – 361.
111. Cooksey RC, Jones D, Gabrielsen S, Huang J, Simcox JA, Luo B, et al. Dietary iron restriction or iron chelation protects from diabetes and loss of beta-cell function in the obese (ob/ob lep−/−) mouse. *Am J Physiol Endocrinol Metab*. 2010; **298:** E1236 – E1243.
112. Minamiyama Y, Takemura S, Kodai S, Shinkawa H, Tsukioka T, Ichikawa H, et al. Iron restriction improves type 2 diabetes mellitus in Otsuka Long-Evans Tokushima fatty rats. *Am J Physiol Endocrinol Metab*. 2010; **298:** E1140 – E1149.
113. Piperno A, Rivolta MR, D'Alba R, Fargion S, Rovelli F, Ghezzi A, et al. Preclinical hypogonadism in genetic hemochromatosis in the early stage of the disease: evidence of hypothalamic dysfunction. *J Endocrinol Invest.* 1992; **15:** 423 – 428.