

Hepatocrinology

Subjects: [Endocrinology & Metabolism](#)

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Hepatocrinology is defined as the bidirectional, complex relationship between hepatic and endocrine physiology and dysfunctions. The scope of hepatocrinology includes conditions of varied etiology (metabolic, infectious, autoimmune, and invasive) that we term as hepato-endocrine syndromes.

cirrhosis

diabetes

endocrine

hepatogenous diabetes

liver

NAFLD

1. Introduction

The subject 'hepatocrinology' is the field of medicine that studies the bidirectional relationship between hepatic and endocrine physiology, as well as dysfunction. The hepato-insular axis is a part of hepatocrine physiology [1]. Endocrine manifestations of liver insufficiency (cirrhosis) and malignancy, and hepatic complications of various endocrine disorders are included. The possible hepatotropic effect of endocrine drugs, pleiotropic endocrine consequences of medicines used in the management of liver disease, and potential exaptation of endocrine agents for use in hepatology form part of this science.

2. The Liver as an Endocrine Organ

The liver secretes various hormones, which mediate glucose metabolism, blood pressure, growth, and hemorheological homeostasis. These include insulin-like growth factor (IGF)-1, betatrophin, and irisin, all of which mediate insulin sensitivity [2][3]. Angiotensinogen, produced by the liver, is the bedrock of the renin-angiotensin-aldosterone system, which contributes to blood pressure maintenance [4]. Hepcidin and thrombopoietin contribute to the regulation of iron metabolism and platelet production, respectively [5][6]. The hepato-insular axis is a well-researched contributor to glucose metabolism and has been described variously as the entero-insular or adipohepato-insular axis [1]. There are several other hormones or their precursors that are synthesized by the liver. Some of the important products are summarized in [Table 1](#) and detailed below.

Table 1. The liver as an endocrine organ.

Action	Hormones	Reference
Hormone synthesis	IGF-1	Bach [2]
	Angiotensinogen	Matsuaska [4]

Action	Hormones	Reference
	Thrombopoietin	Hitchcock [6]
	Hepcidin	Ruchala [5]
	Betatrophin	Raghow [3]
	Proprotein convertase subtilisin-kexin type 9	Yadav [7]
	IGF binding protein 1 to 6	Allard [8]
Hormone action modulation	Sex hormone-binding globulin	Selby [9]
	Thyroid hormone-binding globulin	Schussler [10]
	Transthyretin	Palha [11]
	Corticosteroid binding globulin	Breuner [12]
	Vitamin D binding protein	Bouillon [13]

IGF—insulin-like growth factor.

3. Sexual Dimorphism in Liver Disorders

Many liver diseases show differential gender distribution. NAFLD is more common in men during the reproductive age group, but is more frequent in women after menopause, indicating a possible protective role of estrogen [14]. HCC occurs more commonly in men, while the risk of autoimmune liver diseases such as primary biliary cirrhosis and autoimmune hepatitis is more common in women [15]. Apart from sex hormones, differences in xenobiotics, immune function, genetic alterations, and receptor expression are presumed to drive the dichotomy [16].

4. Endocrine Manifestations of Hepatic Disease

The liver modulates the functioning of the endocrine system directly or indirectly in multiple ways. Liver dysfunction is thus predictably associated with various endocrine disorders. The significant anomalies have been detailed below and depicted in [Figure 1](#).

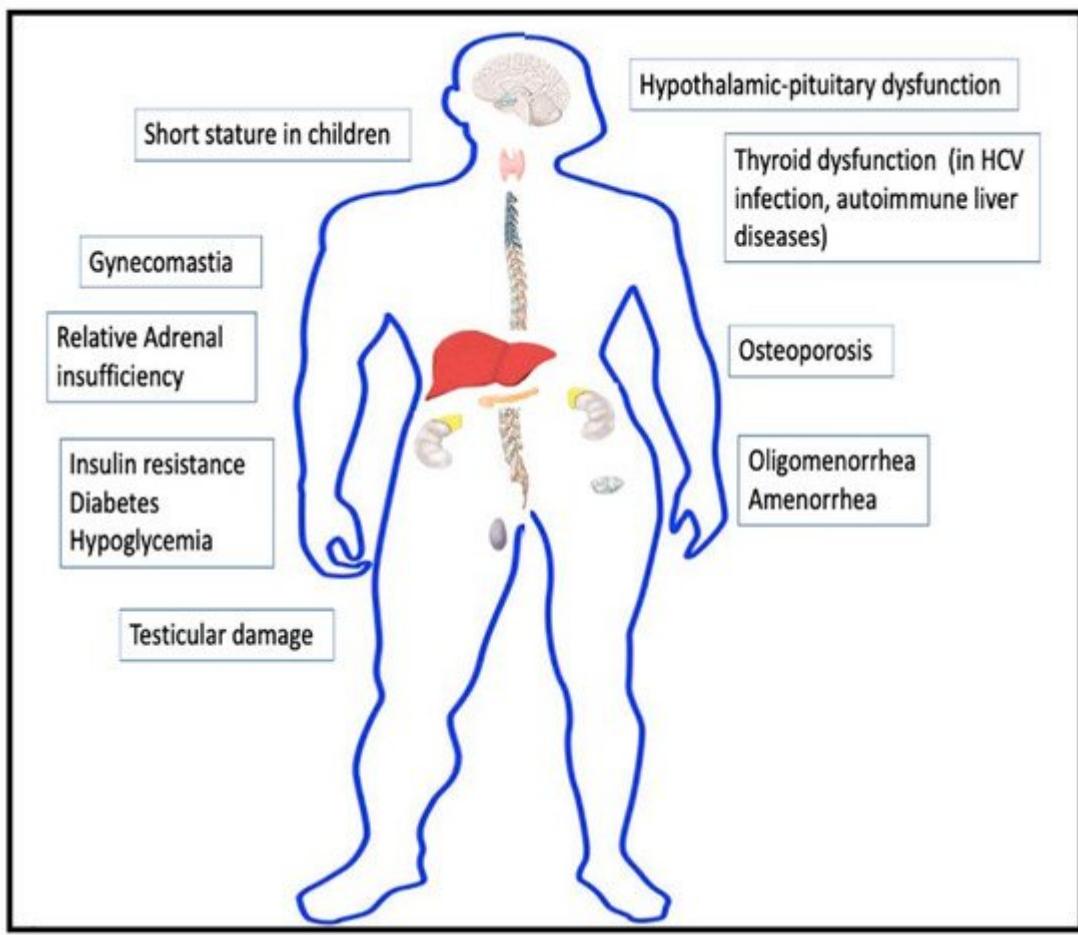


Figure 1. Endocrine manifestations of cirrhosis.

5. Hepatic Manifestations of Endocrine Disease

Endocrine and metabolic diseases are a common cause of hepatic dysfunction. The common endocrine causes of liver dysfunction have been depicted in [Table 2](#). NAFLD resulting from metabolic disorders such as diabetes, obesity, and dyslipidemia has emerged as one of the leading causes of chronic liver disease over the past two decades. Several other hormonal disturbances affect the functioning of the liver directly or indirectly.

Table 2. Hepatic manifestations of endocrine disorders.

Hepatic Manifestation	Endocrine Disorders	References
Non-alcoholic fatty liver disease	Insulin resistance, diabetes, obesity, and dyslipidemia	Watt [17]
Hepatic steatosis or steato-hepatitis	Cushing's syndrome, acromegaly, Graves' disease and other causes of thyrotoxicosis, polycystic ovary syndrome, male hypogonadism, and pheochromocytoma	Lonardo [18]

Hepatic Manifestation	Endocrine Disorders	References
Hepatic metastasis	Adrenal cancer, pancreatic cancer, ovarian and testicular neoplasm, and malignant pheochromocytoma	Ridder [19]
Neonatal cholestasis	Congenital combined pituitary hormone deficiency, congenital hypothyroidism, and HNF1B-MODY (previously MODY-5)	Chan [20], Korkmaz [21]
Acute hepatic congestion (with jaundice)	Myxedema coma	Villalba [22]
Cholestasis	Thyrotoxicosis	Abebe [23]
Congestive hepatomegaly	Thyrotoxic heart failure	Piantanida [24]
Mauriac syndrome	Poorly controlled diabetes mellitus	Subedi [25]

HNF—hepatocyte nuclear factor, MODY—maturity-onset diabetes of young.

6. Sexual Dimorphism in Liver Disorders

Many liver diseases show differential gender distribution. NAFLD is more common in men during the reproductive age group, but is more frequent in women after menopause, indicating a possible protective role of estrogen [14]. HCC occurs more commonly in men, while the risk of autoimmune liver diseases such as primary biliary cirrhosis and autoimmune hepatitis is more common in women [15]. Women also show higher vulnerability to alcohol-related liver diseases [26]. Apart from sex hormones, differences in xenobiotics, immune function, genetic alterations, and receptor expression are presumed to drive the dichotomy [16].

7. Liver Function Biochemical Markers as Predictors of Endocrine Dysfunction

In several studies, liver enzymes have correlated with the development of incident diabetes [27]. γ -glutamyltransferase (GGT) has been proposed as a marker of oxidative stress and is associated with the future risk of diabetes. GGT levels have also been considered an indicator of hepatic fat deposition, which is related to insulin resistance [28]. In several reports, GGT and alanine aminotransferase in early pregnancy predicted the future occurrence of gestational diabetes mellitus [29][30]. [Table 3](#) summarizes the liver enzymes which have been linked to the future development of metabolic disorders.

Table 3. Liver function biochemical markers as predictors of endocrine dysfunction.

Abnormality in Liver Function	Significance	References
Raised GGT	Probable role in the prediction of future risk of diabetes	Kaneko [27]
Elevated ALT	Probable role in the prediction of future risk of diabetes	Kaneko [27]
Elevated ALT and GGT in early pregnancy	Correlates with development of gestational diabetes mellitus	Lee [29], Zhao [30]
Elevated liver enzymes	Possible marker of insulin resistance and metabolic syndrome	Marchesini [31]

GGT— γ -glutamyltransferase, ALT—alanine aminotransferase.

8. Hepato-Endocrine Syndromes

We have used the term “hepato-endocrine syndromes” to describe disorders with a common etiology that manifest as combined hepatic and endocrine dysfunction. The various hepato-endocrine syndromes are enumerated in [Table 4](#). Disorders of iron and copper metabolism such as hemochromatosis and Wilson’s disease are notable examples of this syndrome [32][33]. Polyglandular autoimmune syndromes type 1 and type 2 can develop autoimmune hepatitis and primary biliary cirrhosis, respectively, as their hepatic manifestations [34]. Hepatitis C virus infection can be associated with thyroiditis and hypothyroidism [35].

Table 4. Hepato-endocrine syndromes.

Disease	Hepatic Manifestation	Endocrine Dysfunctions
Metabolic disorders		
Hemochromatosis [32]	Hepatic fibrosis, cirrhosis, and hepatocellular carcinoma	Diabetes, hypopituitarism, secondary hypogonadism, and secondary hypothyroidism
Wilson’s disease [33]	Transaminitis, steatosis, acute hepatitis and acute liver failure (with an associated Coombs-negative hemolytic anemia), chronic hepatitis, and cirrhosis	Fanconi syndrome, distal renal tubular acidosis, nephrolithiasis, gigantism, hypoparathyroidism, pancreatitis, impotence, infertility, and repeated spontaneous abortions
Glycogen storage disorders: Glycogen storage disease I (von Gierke disease)—90% of cases [36]	Glucose-6-phosphatase deficiency in liver and muscle, hepatomegaly, and hepatic adenomas	Hypoglycemia, lactic acidosis, hypertriglyceridemia, and hyperuricemia; short stature, and delayed puberty

Autoimmune disorders		
Polyglandular autoimmune syndrome 1 [34]	Autoimmune hepatitis	Hypoparathyroidism and autoimmune adrenal insufficiency (along with chronic mucocutaneous candidiasis)
Polyglandular autoimmune syndrome 2 [34]	Primary biliary cirrhosis	Addison's disease plus either an autoimmune thyroid disease or type 1 diabetes mellitus associated with hypogonadism, and other endocrinopathies
Infections		
Hepatitis C infection [35]	Chronic hepatitis C, cirrhosis, and hepatocellular carcinoma	Thyroid autoimmunity, hypothyroidism, and higher prevalence of thyroid cancer
Hepatitis B infection [37]	Chronic hepatitis B, cirrhosis, and hepatocellular carcinoma	Increased risk of diabetes mellitus
Malignancy		
Paraneoplastic endocrine syndromes [38]	Hepatocellular carcinoma	Hypoglycemia, hypercholesterolemia, and hypercalcemia

9. Hepatic Effect of Endocrine Drugs

The endocrine drugs can have harmful as well as beneficial effects on the liver. Both anabolic steroids and estrogens can cause cholestasis, hepatic adenoma, focal nodular hyperplasia, and other hepatic disorders [\[39\]\[40\]](#). Acute liver failure has been reported with diverse agents such as propylthiouracil (used for hyperthyroidism) and high doses of methylprednisolone [\[41\]\[42\]](#). Orlistat, a commonly used therapy for weight loss, has also been described to cause subacute and acute liver failure [\[43\]](#).

10. Endocrine Effects of Drugs Used in Hepatology

Spironolactone, commonly used for the management of ascites in patients with cirrhosis, is an anti-androgen which has beneficial effects in PCOS in women, but causes painful gynecomastia in males [\[44\]\[45\]](#). Interferon-alpha used for management of hepatitis C infection can result in thyroid dysfunction [\[46\]](#). Beta-blockers have often been associated with erectile dysfunction [\[47\]](#). [Table 5](#) depicts the common drug interactions in hepatocrinology.

Table 5. Pharmacological interactions in hepatocrinology.

Hepatic Effects of Endocrine Drugs	
Drugs	Adverse Effects

Anabolic androgenic steroid [39]	Hepatic adenoma, hepatocellular carcinoma, cholestasis, and peliosis hepatitis.
Estrogen/oral contraceptive pills [40]	Intrahepatic canalicular cholestasis, hepatic adenomas, focal nodular hyperplasia, hemangioma or hamartoma, peliosis hepatitis, and Budd Chiari syndrome
Tamoxifen [48]	NAFLD
Propylthiouracil, methimazole, carbimazole [41]	Hepatitis, cholestasis, and acute liver failure
Corticosteroids [42]	Hepatic enlargement, steatosis, glycogenosis. NAFLD, exacerbate chronic viral hepatitis, and high doses of intravenous methylprednisolone—acute liver failure (sometimes fatal)
Vasopressin receptor antagonist [49]	Transaminitis and acute liver failure
Orlistat [43]	Cholelithiasis, cholestatic hepatitis, and acute and subacute liver failure

Drugs	Beneficial effects
Pioglitazone [50]	Beneficial effect on NAFLD
GLP-1RA [50]	Possible beneficial effect on NAFLD
SGLT-2 inhibitors [50]	Possible beneficial effect on NAFLD
Saroglitazar [50]	Possible beneficial effect on NAFLD
Corticosteroids [51]	Treatment of autoimmune hepatitis and prevention of rejection of liver transplant
Somatostatin analogs (octreotide and others) [52]	Treatment of variceal bleeding (decreases portal blood flow)
Vasopressin analogs (terlipressin) [52]	Treatment of variceal bleeding (decreases portal blood flow)

Endocrine Effects of Drugs Used in Hepatology

Drugs	Adverse effects
Spironolactone [45]	Gynaecomastia, and hypogonadism in men
Beta-blockers [47]	Erectile dysfunction

Interferon-alpha [46]	Hypothyroidism, autoimmune (Hashimoto's) thyroiditis, destructive thyroiditis, and Graves' disease
Drugs	Beneficial effects
Ursodeoxycholic acid [53]	Possible beneficial effect in metabolic syndrome
Spironolactone [44]	Treatment of PCOS

NAFLD—non-alcoholic fatty liver disease, PCOS—polycystic ovary syndrome, GLP-1RA glucagon-like peptide receptor agonist, SGLT-2—sodium glucose cotransporter-2, GGT— γ -glutamyltransferase, and ALT—alanine aminotransferase.

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