Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.14.4111

World J Gastroenterol 2008 July 14; 14(26): 4111-4119
World Journal of Gastroenterology ISSN 1007-9327
© 2008 The WJG Press. All rights reserved.

EDITORIAL

Liver in systemic disease

Yukihiro Shimizu

Yukihiro Shimizu, Division of Internal Medicine, Center for Gastroenterology and Hepatology, Kyoto Katsura Hospital, 17 Yamada-Hirao, Nishikyo, Kyoto 615-8256, Japan
Author contributions: Shimizu Y summarized and reviewed the previous reports on liver injury in systemic disease and wrote the manuscript alone.
Correspondence to: Yukihiro Shimizu, MD, PhD, Division head, Division of Internal Medicine, Center for Gastroenterology and Hepatology, Kyoto Katsura Hospital, 17 Yamada-Hirao, Nishikyo, Kyoto 615-8256, Japan. yukihiro@katsura-hp.jp
Telephone: +81-75-3915811 Fax: +81-75-3810090
Received: March 28, 2008 Revised: May 9, 2008
Accepted: May 16, 2008
Published online: July 14, 2008

Abstract

Potential causes of abnormal liver function tests include viral hepatitis, alcohol intake, nonalcoholic fatty liver disease, autoimmune liver diseases, hereditary diseases, hepatobiliary malignancies or infection, gallstones and drug-induced liver injury. Moreover, the liver may be involved in systemic diseases that mainly affect other organs. Therefore, in patients without etiology of liver injury by screening serology and diagnostic imaging, but who have systemic diseases, the abnormal liver function test results might be caused by the systemic disease. In most of these patients, the systemic disease should be treated primarily. However, some patients with systemic disease and severe liver injury or fulminant hepatic failure require intensive treatments of the liver.

© 2008 The WJG Press. All rights reserved.

Key words: Abnormal liver function tests; Jaundice; Systemic disease

Peer reviewer: Guang-Cun Huang, MD, PhD, Nationwide Children's Hospital and The Ohio State University, Center for Cell & Developmental Biology, The Research Institute at Nationwide Children's Hospital and The Ohio State University, 700 Childrens Drive, Columbus OH 43205, United States

Shimizu Y. Liver in systemic disease. *World J Gastroenterol* 2008; 14(26): 4111-4119 Available from: URL: http://www.wjgnet.com/1007-9327/14/4111.asp DOI: http://dx.doi.org/10.3748/wjg.14.4111

INTRODUCTION

Potential causes of abnormal liver function tests include viral hepatitis, alcohol intake, nonalcoholic fatty liver disease, autoimmune liver diseases and hereditary diseases such as hemochromatosis, α_1-antitrypsin deficiency and Wilson's disease. Many patients with liver injury are likely to be treated with several drugs, increasing the possibility that their liver injuries are drug-induced. Some patients with liver injury, however, have underlying systemic diseases, which may also affect their livers. Knowledge of liver involvement in systemic diseases is important for the accurate diagnosis of liver injury and to avoid unnecessary examination and treatment. This review will describe liver injury caused by various systemic diseases.

CARDIOVASCULAR DISEASES

Ischemic hepatitis

The pathophysiology of ischemic hepatitis, also known as "shock liver", is poorly understood[1]. Patients usually show rapid (within 24-48 h) and dramatic transient increases in serum aminotransferase, lactate dehydrogenase (LDH) levels and bilirubin following periods of hemodynamic instability or hypoxia. Three features distinguish ischemic hepatitis from acute viral hepatitis: LDH elevation is more marked in ischemic than in viral hepatitis; serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations rapidly return to normal in ischemic hepatitis, usually within 7-10 d; and ischemic hepatitis is more often complicated by renal damage[2]. Ischemic hepatitis has several etiologies (Table 1)[2].

Liver congestion

Liver congestion is caused by acute or chronic right-sided heart failure and is manifested by hepatomegaly (95%-99%), ascites (7%-49%), splenomegaly (12%-25%) and/or jaundice (< 20%)[3,4]. In addition, patients often show signs indicative of heart failure, including peripheral edema and pleural effusion. Liver function tests show that serum bilirubin is elevated, usually to 1-5 mg/dL and mostly in the unconjugated form, in 24%-81% of patients, depending on the severity of heart failure[3-5]. Bilirubin concentrations rapidly return to normal 3-7 d after improvement of right-sided heart failure. In addition, 3%-50% of patients with heart failure show elevated levels of serum aminotransferases, with the elevation of AST more marked than that of ALT[3-5]. Elevated serum alkaline phosphatase (ALP) is observed in 10%-20% of patients with right-sided heart failure, but these levels return to normal within 1 wk after improvement of heart failure[3-5].

Table 1 Etiologies of ischemic hepatitis[2]

Etiologies of ischemic hepatitis
Left ventricular failure
Acute myocardial infarction
Cardiac arrhythmia
Prosthetic valvular dysfunction
Cardiomyopathy
Pericardial tamponade
Other causes of shock
Trauma
Burns
Dehydration
Hemorrhage

Cardiac cirrhosis

Cardiac cirrhosis may occur after longstanding hepatic congestion, but its incidence is relatively low. Although liver cirrhosis has no characteristic biochemical markers, a multivariate analysis found that elevated concentrations of AST and bilirubin are prognostic of poor outcome[6].

HEATSTROKE

The liver is extremely sensitive to thermal injury and is a frequent site of tissue injury in patients with heatstroke, with almost all of these patients experiencing liver injury[7]. Elevated serum ALT concentration is the most common feature in patients with heatstroke, and may lead to acute hepatic failure[8]. Liver function tests usually return to normal after 2 wk, but may remain elevated after 1 mo[9].

CONNECTIVE TISSUE DISEASES

Connective tissue diseases often involve the liver, and various forms of hepatic involvement have been reported. Laboratory markers and liver diseases associated with connective tissue diseases are summarized in Table 2[10,11]. For example, liver disease has been shown to be a common complication of systemic lupus erythematosus (SLE). Elevated serum ALT has been observed in 21% of patients with SLE[12], and 4.4% of patients with SLE may have serious chronic liver diseases, including chronic active hepatitis and liver cirrhosis[13-16]. The most common liver histologic manifestation of SLE is steatosis, which may not be associated with corticosteroid therapy[17]. It is important to distinguish lupus-related chronic hepatitis from autoimmune hepatitis (AIH), because patients with the latter often rapidly progress to liver cirrhosis unless they are treated with appropriate and sufficient doses of corticosteroids. Inasmuch as corticosteroid treatment can improve liver biochemical abnormalities in either disease, a response to the drug does not contribute to the differential diagnosis. The presence of anti-smooth muscle antibody, which is found in patients with AIH but not in those with lupus-related liver disease, may be helpful for distinguishing these two diseases[18]. There have been reports of patients with overlapping SLE and autoimmune hepatitis[13-16], thus confusing the diagnosis of liver disease in SLE patients. Criteria are needed for the differential diagnosis of AIH and lupus-related liver disease in patients with SLE.

Table 2 Connective tissue disease-associated abnormal liver function tests and liver diseases[10,11]

Connective tissue disease	Abnormal liver function tests	Liver disease or histology
Juvenile rheumatoid arthritis	Elevated aminotransferases	Drug hepatotoxicity Massive hepatomegaly Infiltration of portal tracts by chronic inflammatory cells Acute necro-inflammatory disease
Felty syndrome	Elevated ALP and aminotransferases	Chronic hepatitis Drug hepatotoxicity Nodular regenerative hyperplasia Portal fibrosis Sinusoidal lymphocytosis Amyloidosis Macronodular cirrhosis Hepatomegaly
Rheumatoid arthritis	Elevated ALP, correlate with severity of arthritic activity	Drug hepatotoxicity Autoimmune chronic hepatitis (type 1) Nodular regenerative hyperplasia Primary biliary cirrhosis Amyloidosis Spontaneous hepatic rupture/ Necrotizing arteritis Steatosis
Polymyalgia rheumatica	Elevated ALP and aminotransferases	Drug hepatotoxicity Steatosis Lymphocytic infiltration of portal tracts Granulomas Hyperplasia of perisinusoidal stellate cells Primary biliary cirrhosis
Sjögren's syndrome	Elevated ALP and aminotransferases	Primary; 7% have liver dysfunction, mostly PBC Secondary; 40%-70% have PBC
Scleroderma	Hepatic involvement is low; Elevated ALP, mild elevation of aminotransferases and bilirubin	Drug hepatotoxicity CREST syndrome (PBC) Spotty calcification Idiopathic portal hypertension Cirrhosis Nodular regenerative hyperplasia Hepatomegaly
Systemic lupus erythematosus	Elevated aminotransferases in up to 50% of patients	Drug hepatotoxicity Autoimmune chronic hepatitis (type 1) Venous congestion Nodular regenerative hyperplasia Hepatic infarction Steatosis Venous thrombosis Granulomatous hepatitis Centrilobular necrosis Cirrhosis
Adult Still's disease	Elevated ALP and aminotransferases	Moderate portal mononuclear cell infiltration with occasional focal hepatocyte necrosis

HEMATOLOGICAL DISEASES

Hodgkin disease

Liver infiltration of malignant cells has been reported in 14% of patients with Hodgkin disease, and hepatomegaly in 9% of patients with stage Ⅰ-Ⅱ and in 45% of patients with stage Ⅲ-Ⅳ disease[17]. In addition, mild elevations of aminotransferases and moderate elevation of ALP can occur, due to tumor infiltration or extrahepatic bile duct obstruction[17]. However, cholestasis in zone 3, which was not associated with extrahepatic obstruction or tumor infiltration, has been described; this cholestasis may be due to vanishing bile duct syndrome[18].

Non-Hodgkin lymphoma

Lymphoma cell infiltration of the liver is more common in non-Hodgkin than in Hodgkin disease, with 16%-43% of non-Hodgkin patients showing hepatic involvement[17]. Extrahepatic obstruction is also more common in non-Hodgkin than in Hodgkin disease. Moreover, hepatic infiltration is more common in low-grade B-cell lymphomas (small cell) than in high-grade (diffuse large B-cell, T-cell histiocytic) lymphomas[19]. Liver function tests show mild to moderate elevations in serum ALP, and hepatomegaly may occur[17]. Although liver involvement in both Hodgkin and non-Hodgkin lymphomas may present as acute hepatic failure[20-25], liver transplantation should be avoided[26]. Jaundice due to non-Hodgkin lymphoma can be distinguished from that due to viral hepatitis or drug hepatotoxicity by the presence of liver enlargement and lactic acidosis in lymphoma[27].

Chronic lymphoid leukemia (CLL)

Patients with CLL often show mild to moderate liver enlargement and extensive lymphocytic infiltration in the portal tracts, with functional impairment of the liver in late stages[28,29].

Hairy cell leukemia

Leukemia cells often infiltrate the liver, in both the portal tracts and sinusoids, and liver enlargement has been observed in up to 40% of patients with this disease[30].

Acute leukemia

Although hepatic involvement in acute leukemia is usually mild and silent at the time of diagnosis[27], a post mortem study showed liver infiltration in > 95% of ALL and up to 75% of AML patients[31]. In ALL, infiltration was confined to the portal tracts, whereas, in AML, infiltration was observed in both portal tracts and sinusoids. Massive leukemic cell infiltration of the liver may present as fulminant hepatic failure[32]. In patients with acute leukemia, drug-induced liver injury and bacterial or fungal infections may also affect the liver.

Multiple myeloma

Hepatomegaly has been observed in 15%-40% of patients with multiple myeloma and may sometimes be accompanied by splenomegaly[33,34].

Primary myelofibrosis

Liver involvement is common in patients with primary myelofibrosis, and liver enlargement is observed in almost all patients. The mechanisms of liver involvement have been associated with extramedullary hematopoiesis, increased hepatic blood flow and hemosiderosis caused by multiple blood transfusions[27]. Ascites and esophageal varices secondary due to portal hypertension has been found in 7% of these patients[35,36] and nodular regenerative hyperplasia of the liver following obstruction of intrahepatic portal vein branches may augment the portal hypertension[37]. The most common liver function abnormality in patients with primary myelofibrosis is elevated ALP, which has a frequency of 40%-60% and which may be associated with the severity of sinusoidal dilatation[38].

Polycythemia vera

Although direct liver involvement is uncommon, some patients may present with acute or chronic Budd-Chiari syndrome[39].

Chronic myeloid leukemia (CML)

About 50% of patients with CML show mild to moderate hepatomegaly at presentation, with no liver function abnormalities[40]. At the time of blastic crisis, however, liver sinusoidal infiltration by immature cells may lead to liver enlargement and elevated serum ALP levels[41].

Myelodysplasias

In patients with sideroblastic or refractory anemia, iron deposition in the liver may occur due to repeated transfusion or decreased iron utilization by bone marrow[27].

Sickle-cell disease

The liver is commonly involved in sickle-cell disease. This may be due to iron overload caused by multiple blood transfusions, gallstones, or cardiac dysfunction due to secondary hemochromatosis[42].

Thalassemia

The major cause of liver injury in patients with thalassemia is hemochromatosis due to ineffective erythropoiesis, with massive iron deposits found in the liver[27].

LUNG DISEASES

Pneumonia

Lobar pneumonia caused by *Legionella pneumophila, Mycoplasma pneumoniae* or *Pneumococcus* may be associated with elevated concentrations of serum aminotransferase and bilirubin[43].

Jaundice has been observed in 3%-25% of patients with *Pneumococcus* pneumonia[44], often developing between days 3 and 6 of illness.

In *Legionnaire's* disease, liver function tests are likely to show abnormalities, with elevated concentration

of serum ALP and aminotransferase in up to 50% of patients[45].

Mycoplasma pneumoniae is a frequent cause of community-acquired pneumonia. Liver involvement is not common, but some patients may have elevated levels of serum aminotransferases[43]. Cholestatic hepatitis and mild hepatitis without pneumonia have been described[43].

Cytomegalovirus pneumonia can also result in jaundice and elevated levels of ALP and aminotransferases[46].

Chronic pulmonary disease

Serum bilirubin, ALT, γ-glutamyl transpeptidase (GGT) and ALP may be elevated in patients with chronic pulmonary disease or status asthmatics[47-49], and these liver abnormalities may be associated with secondary heart failure or hypoxia.

RENAL DISEASES

Even in the absence of liver metastasis, renal cancer causes hepatomegaly and abnormal liver function test results. Following tumor resection, however, these liver abnormalities return to normal, suggesting that the previously observed abnormalities were caused by a hepatotoxic hormone secreted from the tumor[50].

SYSTEMIC INFECTION-BACTEREMIA AND SEPSIS

Cholestasis is a common complication in patients with extrahepatic bacterial infection and sepsis, regardless of whether the infectious agent is gram-negative (*E.coli* and *Klebsiella*) or gram-positive (*S aureus*)[51,52]. Proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), as well as nitric oxide, are thought to induce cholestasis by inhibiting the canalicular excretion of conjugated bilirubin[53]. Liver biopsy may show mild portal inflammation, but bile ducts often appear normal and there is usually no cholangitis[54].

Laboratory findings in sepsis include mild elevation of ALP (mostly 1 to 3 times the ULN) and modest elevation of ALT. Peak serum bilirubin concentrations typically range from 5 to 10 mg/dL, but levels as high as 30 to 50 mg/dL have been reported[31]. Importantly, the serum concentrations of ALP and bilirubin may be discordant, with deeply jaundiced patients often having normal ALP levels, while anicteric patients may show marked elevation of ALP or GGT[55-57]. Compared with infected patients without bacteremia, those with bacteremia had significantly higher serum levels of GGT and ALP and significantly lower serum concentrations of albumin, cholesterol and cholinesterase. These alterations were observed within several days after the onset of bacteremia, but concentrations returned to normal following adequate treatment of the infection[52]. Although the major pathogens were *S aureus* and *E.coli*, *P aeruginosa* infection may cause cholestasis more frequently than other organisms, with 26% to 52% of patients severely infected with *P aeruginosa* having jaundice[58]. At autopsy, these patients showed periportal cholestasis with minimal liver cell damage.

LIVER DAMAGE IN INFECTION BY SPECIFIC PATHOGENS

Clostridium perfringens infection

C perfringens may directly affect the liver by forming an abscess or causing necrotizing massive gas gangrene of the liver, leading to fulminant hepatic failure[59].

Salmonella typhi infection

While sepsis can cause liver dysfunction, it can also occur following *Salmonella typhi* infection, a condition known as *Salmonella* hepatitis[60]. Although severe elevation of liver function tests is rare, jaundice has been observed in 33% of these patients. Although the clinical features of *Salmonella* hepatitis may be identical to those of acute viral hepatitis, these diseases may be distinguished by the ALT/LDH ratio, which is < 4.0 in *Salmonella* hepatitis, significantly lower than the ratio in acute viral hepatitis, > 5.0[61].

Lyme disease

Hepatic involvement is common in Lyme disease caused by *Borrelia burgdorferi*, and mild elevations of GGT and aminotransferase are commonly observed especially in patients with early stage disease[62,63].

Q fever

Nearly 50% of patients with Q fever had accompanying hepatitis, but the liver function abnormalities were nonspecific. Although these patients usually show anicteric hepatitis, one third may have jaundice if the disease is prolonged[64].

Syphilis

Acute cholestatic syphilitic hepatitis, sometimes accompanied by jaundice, has been reported in patients with secondary syphilis[65]. Patients with tertiary syphilis may present with gummas formation in the liver, which resemble metastatic tumors[66].

Campylobacter infection

Mild to severe liver biochemical abnormalities have been observed following infection with *Campylobacter* organisms[67].

Chlamydia or Neisseria infection

Perihepatitis has been observed in patients infected with *Chlamydia trachomatis*[68] and *Neisseria gonorrhoeae*[69], with the formation of liver granulomas in the former[65].

HIV infection

Liver injury in patients with HIV infection can be caused by HIV itself, by coinfection with hepatitis viruses such as HBV and HCV, or by hepatic involvement of

Table 3 Liver involvement in deep fungal infections[73]

Liver involvement in deep fungal infections
Opportunistic mycoses
Candidiasis-includes hepatosplenic candidiasis
Cryptococcosis
Less common: aspergillosis, mucormycosis, trichosporonosis
Pathogenic mycoses
Histoplasmosis-disseminated histoplasmosis
Paracoccidiodomycoses
Less common: coccidioidomycosis, african histoplasmosis, blastomycosis, penicilliosis

systemic infections, including *M tuberculosis*, *M avium complex*, *Toxoplasma gondii*, or *Cryptosporidium*. In addition, liver injury in HIV-infected patients may be due to the toxicities of drugs prescribed for the treatment of HIV or coinfected microbes. In addition, biliary tract injuries caused by tuberculosis, *M.avium* and *Cryptosporidium* have been reported[70].

Mycobacteria infection

Liver involvement is frequent in patients with mycobacterial infections, not only with *Mycobacterium tuberculosis* infection, but also with *M avium intracellulare* or *M genavense* infection[65]. The clinical spectrum of liver disease due to *Mycobacterium spp*. ranges from the absence of symptoms to liver failure, with multiple granulomas in the parenchyma of the liver being the most common lesion[71]. These patients show elevated serum ALP concentrations and hepatomegaly. Although the number of intrahepatic granulomas is greater in patients with than without disseminated military tuberculosis, hepatic tuberculosis can occur, even in the absence of apparent tuberculosis elsewhere[72].

Fungal infection

The liver is often involved in deep fungal infections, possibly due to enrichment of the blood flow through the liver or the invasion of fungi, including *C albicans* and *C. tropicans*, into the liver from the gut by penetrating through degenerated barriers of gastrointestinal mucosa[73]. Patients with liver involvement of fungal infection may show elevated serum concentrations of ALP and GGT, due to the formation of multiple small abscesses or granulomas in the liver. Liver involvement following deep fungal infections is summarized in Table 3[73].

ACUTE HEPATIC FAILURE CAUSED BY VIRUSES OTHER THAN HEPATITIS A TO E

The major causes of acute hepatic failure include drugs, hepatitis A, hepatitis B, and hepatitis E. Although Epstein-Barr virus and cytomegalovirus can also cause severe hepatitis during primary infection, other microbes, which mainly affect other organs, can cause acute hepatic failure. Among these are *Salmonella paratyphi A*[74], herpes simplex virus[75,76], parvovirus B19[77], coxsackie virus B2[78], human herpesvirus-6[79], Varicella-Zoster virus[80], and Dengue virus[81]. Parvovirus B19 and human herpesvirus-6 are often found in patients with non-A to non-E acute hepatic failure.

TOTAL PARENTERAL NUTRITION (TPN)

TPN may cause steatosis or cholestasis, and liver disease is more severe in infants than in adults. Elevated serum aminotransferase concentrations are common during the first 1-3 wk of TPN, and bilirubin increases in some adults after 10 wk or more of TPN[82-84]. Chronic cholestasis has been observed in 55% of patients receiving TPN for at least 2 years[85], and cholestasis can lead to acalculous and calculous cholecystitis or TPN-induced cholelithiasis[86].

ENDOCRINE DISEASES

Thyroid disease

Patients with hyperthyroidism frequently experience liver injury, which may be caused by increased hepatocyte oxygen demand without an associated increase in hepatic blood flow. Liver injury can be either cholestatic or hepatocellular. Up to 64% of these patients show elevated serum ALP, and up to 35% show elevated ALT. Interestingly, only 17% of these patients show elevated GGT[17], and most of the increased ALP is bone-derived[87].

In contrast to hyperthyroidism, liver biochemistry abnormalities are less prominent in patients with hypothyroidism. However, modest elevations in serum AST and ALT have been reported in 84% and 60%, respectively, of patients with hypothyroidism[88]. Some patients may show low serum ALP[87], but their most characteristic symptom is ascites, which is caused by unknown mechanisms[87]. In addition, cholestatic jaundice has been described in case reports of patients with severe hypothyroidism[17].

Cushing syndrome

Hypercortisolism causes fatty infiltration of the liver in half of the patients, which may progress to NASH. The prevalence of NASH in these patients has been estimated to be 20% to 50%[89].

Adrenal insufficiency

Elevated serum aminotransferase concentrations have been reported in patients with adrenal insufficiency; these abnormalities usually resolve with appropriate hormone replacement[90,91].

Diabetes mellitus

Elevated liver chemistries have been observed in 10%-20% of patients with DM[92,93], more frequently in patients with type 2 than type 1 DM[94]. One study reported that 16.5%, 9%, 11% and 6% of these patients had elevations in serum GGT, ALP, ALT and AST, respectively. Non-alcoholic fatty liver disease is a complication in 32% to 78% of patients with type 2

DM, and 50% of these patients may have non-alcoholic steatohepatitis (NASH)[95,96]. NASH in DM patients may lead to liver cirrhosis and eventually to hepatocellular carcinoma[94,97].

POSTOPERATIVE JAUNDICE

Jaundice often occurs after surgery, especially after cardiac surgery; of the latter, approximately 26.5% show conjugated hyperbilirubinemia[98]. Factors thought to contribute to the development of jaundice after surgery include: (1) Liver congestion due to preexisting right-sided heart failure; (2) Degree of perioperative hypotension and hypoxia; (3) Destruction of transfused erythrocytes; (4) Hemolysis secondary to mechanical prostheses; (5) Type of operation-The incidence of postoperative jaundice is dependent on the type of operation. For example, patients who underwent mitral valve replacement or multiple valve surgery had a higher rate of jaundice than those who underwent coronary bypass graft surgery; (6) Perioperative infection; (7) Resorption of hematoma; (8) Worsening of jaundice in Gilbert's syndrome-Gilbert's syndrome is the most common form of inherited hyperbilirubinemia, with 5% to 10% of Caucasians and Japanese estimated to have this syndrome. Although serum bilirubin levels are usually below 3 mg/dL, with the unconjugated form being dominant, jaundice may be worsened by a stress caused by surgery or infection; (9) Total parenteral nutrition; (10) Drug-induced liver injury, and (11) Benign postoperative intrahepatic cholestasis.

Postoperative jaundice usually occurs within 1-2 wk after major surgery. Serum concentrations of mainly conjugated bilirubin may increase to 40 mg/dL, but these resolve within a few days to weeks without specific treatment[99].

GASTROINTESTINAL DISEASES

Abnormal liver function test results are observed in over 50% of patients with inflammatory bowel diseases requiring surgery. The hepatobiliary diseases accompanying ulcerative colitis and Crohn's disease are shown in Table 4[100].

Patients who undergo jejunoileal resection for the treatment of severe obesity may experience liver damage[101]. The liver often shows NASH, leading to liver cirrhosis and liver failure. Similar liver injuries have been observed in patients undergoing gastrectomy *via* Billroth-Ⅱ reconstruction. Bacterial overgrowth in the blind-loop of the intestine can induce endotoxin and intrinsic ethanol[102,103], leading to Kupffer cell activation and hepatocyte damage.

GRANULOMA FORMATION IN THE LIVER

Several systemic diseases and drugs have been shown to induce granulomas in the liver, causing liver enlargement. The most consistently abnormal liver biochemistry result is elevated serum ALP. The diagnosis and causes of hepatic granulomas may be determined by a histological examination of the liver. Five etiological categories have been identified[104]: (1) Immunological: Sarcoidosis, primary biliary cirrhosis, giant cell hepatitis, Wegener's granulomatosis, chronic granulomatous disease and allergic granulomatosis; (2) Infectious: Hepatitis C virus, cytomegalovirus, Epstein-Barr virus, tuberculosis, *Mycobacterium avium-intracellulare* in patients with HIV infection, leprosy, brucellosis, typhoid fever, Whipple's disease, tularaemia, yersiniosis, cat-scratch disease, histoplasmosis, blastomycosis, coccidiomycosis, candidiasis, Q fever, leishmaniasis, toxoplasmosis, syphilis, and schistosomiasis; (3) Medications: Penicillins, diphenylhydantoin and allopurinol; (4) Neoplastic: Hodgkin's disease and hypernephroma, and (5) Foreign body: Beryllium, suture material used in operation and thorotrast.

Table 4 Hepatobiliary disorders associated with inflammatory bowel disease[100]

Hepatobiliary disorders	Ulcerative colitis	Crohn's disease
Primary sclerosing cholangitis (PSC)	+	+
Large duct PSC	+	+
Small duct PSC (pericholangitis)	+	+
Cirrhosis	+	+
Hepatocelullar carcinoma	+	+
Cholangiocarcinoma	+	+
Miscellaneous disorders		
Fatty liver	+	+
Granulomas		+
Amyloidosis		+
Hepatic abscess		+
Gallstones		+
Autoimmune hepatitis	+	

AMYLOIDOSIS

Hepatic involvement has been demonstrated in about one-fifth of patients with AA amyloidosis and about half of those with the AL type, and liver function tests can remain normal even in patients with substantial amyloid deposits and hepatomegaly. Elevated serum ALP and GGT occur first in patients with massive amyloid deposits, followed by modest elevations of serum AST and ALT[105].

CONCLUSION

Abnormal liver function often occurs in patients without hepatitis virus infection and without excessive alcohol intake. Although US, CT or MR imaging should be used to assess the occurrence of fatty liver disease, hepatobiliary malignancies or infection and gallstones, diagnosis of autoimmune liver disease, especially with atypical presentation, is sometimes difficult. Moreover, intake of drugs including herbal medicines or supplemental nutrients may cause liver injury. However, abnormal liver function tests do not necessarily indicate serious liver disease. Asymptomatic patients with isolated, mild elevation of unconjugated bilirubin (e.g. Gilbert's syndrome) or GGT generally do not have liver disease and do not require further examination[106]. In

contrast, the liver may be involved in systemic diseases that mainly affect other organs. Therefore, in patients without etiology of liver injury by screening serology and diagnostic imaging, but who have systemic diseases, the abnormal liver function test results might be caused by the systemic disease. In most of these patients, the systemic disease should be treated primarily. However, some patients with systemic disease and severe liver injury or fulminant hepatic failure require intensive treatments of the liver.

REFERENCES

1 **Kay PS**, Keeffe EB. Cardiac disease and the liver. In: Gitlin N editor. The Liver and Systemic Disease. Hong Kong: Pearson Professional Limited, 1997: 1-16
2 **Gitlin N**, Serio KM. Ischemic hepatitis: widening horizons. *Am J Gastroenterol* 1992; **87**: 831-836
3 **Richman SM**, Delman AJ, Grob D. Alterations in indices of liver function in congestive heart failure with particular reference to serum enzymes. *Am J Med* 1961; **30**: 211-225
4 **Dunn GD**, Hayes P, Breen KJ, Schenker S. The liver in congestive heart failure: a review. *Am J Med Sci* 1973; **265**: 174-189
5 **Sherlock S**. The liver in heart failure; relation of anatomical, functional, and circulatory changes. *Br Heart J* 1951; **13**: 273-293
6 **Tiukinhoy-Laing S**, Blei AT, Gheorghiade M. The liver in cardiovascular disease. In: Rodés J, Benhaumou JP, Blei AT, Reichen J, Rizzetto M, editors. Textbook of Hepatology. 3rd ed. Oxford: Blackwell Publishing, 2007: 1609-1615
7 **Rubel LR**, Ishak KG. The liver in fatal exertional heatstroke. *Liver* 1983; **3**: 249-260
8 **Weigand K**, Riediger C, Stremmel W, Flechtenmacher C, Encke J. Are heat stroke and physical exhaustion underestimated causes of acute hepatic failure? *World J Gastroenterol* 2007; **13**: 306-309
9 **Kew M**, Bersohn I, Seftel H, Kent G. Liver damage in heatstroke. *Am J Med* 1970; **49**: 192-202
10 **Gitlin N**. Connective tissue diseases and the liver. In: Gitlin N editor. The Liver and Systemic Disease. Hong Kong: Pearson Professional Limited, 1997: 115-135
11 **Abraham S**, Begum S, Isenberg D. Hepatic manifestations of autoimmune rheumatic diseases. *Ann Rheum Dis* 2004; **63**: 123-129
12 **Runyon BA**, LaBrecque DR, Anuras S. The spectrum of liver disease in systemic lupus erythematosus. Report of 33 histologically-proved cases and review of the literature. *Am J Med* 1980; **69**: 187-194
13 **Tojo J**, Ohira H, Abe K, Yokokawa J, Takiguchi J, Rai T, Shishido S, Sato Y, Kasukawa R. Autoimmune hepatitis accompanied by systemic lupus erythematosus. *Intern Med* 2004; **43**: 258-262
14 **Usta Y**, Gurakan F, Akcoren Z, Ozen S. An overlap syndrome involving autoimmune hepatitis and systemic lupus erythematosus in childhood. *World J Gastroenterol* 2007; **13**: 2764-2767
15 **Iwai M**, Harada Y, Ishii M, Tanaka S, Muramatsu A, Mori T, Nakashima T, Okanoue T, Hirohata S. Autoimmune hepatitis in a patient with systemic lupus erythematosus. *Clin Rheumatol* 2003; **22**: 234-236
16 **Lu MC**, Li KJ, Hsieh SC, Wu CH, Yu CL. Lupus-related advanced liver involvement as the initial presentation of systemic lupus erythematosus. *J Microbiol Immunol Infect* 2006; **39**: 471-475
17 **Ross A**, Friedman LS. The liver in systemic disease. In: Bacon BR, O'Grady JG, Di Bisceglie AM, Lake JR, editors. Comprehensive Clinical Hepatology. 2nd ed. Philadelphia: Mosby Elsevier Ltd, 2006: 537-547
18 **Hubscher SG**, Lumley MA, Elias E. Vanishing bile duct syndrome: a possible mechanism for intrahepatic cholestasis in Hodgkin's lymphoma. *Hepatology* 1993; **17**: 70-77
19 **Jaffe ES**. Malignant lymphomas: pathology of hepatic involvement. *Semin Liver Dis* 1987; **7**: 257-268
20 **Vardareli E**, Dundar E, Aslan V, Gulbas Z. Acute liver failure due to Hodgkin's lymphoma. *Med Princ Pract* 2004; **13**: 372-374
21 **Dourakis SP**, Tzemanakis E, Deutsch M, Kafiri G, Hadziyannis SJ. Fulminant hepatic failure as a presenting paraneoplastic manifestation of Hodgkin's disease. *Eur J Gastroenterol Hepatol* 1999; **11**: 1055-1058
22 **Rowbotham D**, Wendon J, Williams R. Acute liver failure secondary to hepatic infiltration: a single centre experience of 18 cases. *Gut* 1998; **42**: 576-580
23 **Emile JF**, Azoulay D, Gornet JM, Lopes G, Delvart V, Samuel D, Reynes M, Bismuth H, Goldwasser F. Primary non-Hodgkin's lymphomas of the liver with nodular and diffuse infiltration patterns have different prognoses. *Ann Oncol* 2001; **12**: 1005-1010
24 **Morali GA**, Rozenmann E, Ashkenazi J, Munter G, Braverman DZ. Acute liver failure as the sole manifestation of relapsing non-Hodgkin's lymphoma. *Eur J Gastroenterol Hepatol* 2001; **13**: 1241-1243
25 **Yeshurun M**, Isnard F, Garderet L, Rambeloarisoa J, Prevot S, Carbonell N, Najman A. Acute liver failure as initial manifestation of low-grade non-Hodgkin's lymphoma transformation into large-cell lymphoma. *Leuk Lymphoma* 2001; **42**: 555-559
26 **Woolf GM**, Petrovic LM, Rojter SE, Villamil FG, Makowka L, Podesta LG, Sher LS, Memsic L, Vierling JM. Acute liver failure due to lymphoma. A diagnostic concern when considering liver transplantation. *Dig Dis Sci* 1994; **39**: 1351-1358
27 **Bruguera M**, Miquel R. The effect of hematological and lymphatic diseases on the liver. In: Rodés J, Benhaumou JP, Blei AT, Reichen J, Rizzetto M, editors. Textbook of Hepatology. 3rd ed. Oxford: Blackwell Publishing, 2007: 1662-1670
28 **Schwartz JB**, Shamsuddin AM. The effects of leukemic infiltrates in various organs in chronic lymphocytic leukemia. *Hum Pathol* 1981; **12**: 432-440
29 **Wilputte JY**, Martinet JP, Nguyen P, Damoiseaux P, Rahier J, Geubel A. Chronic lymphocytic leukemia with portal hypertension and without liver involvement: a case report underlining the roles of increased spleno-portal blood flow and "protective" sinusoidal vasoconstriction. *Acta Gastroenterol Belg* 2003; **66**: 303-306
30 **Yam LT**, Janckila AJ, Chan CH, Li CY. Hepatic involvement in hairy cell leukemia. *Cancer* 1983; **51**: 1497-1504
31 **Thiele DL**. Hepatic manifestations of systemic disease and other disorders of the liver. In: Feldman M, Friedman LS, Sleisenger MH, editors. Sleisenger & Fordtran's Gastrointestinal and Liver Disease. 7th ed. Philadelphia: Elsevier Science, 2002: 1603-1619
32 **Litten JB**, Rodriguez MM, Maniaci V. Acute lymphoblastic leukemia presenting in fulminant hepatic failure. *Pediatr Blood Cancer* 2006; **47**: 842-845
33 **Perez-Soler R**, Esteban R, Allende E, Tornos Salomo C, Julia A, Guardia J. Liver involvement in multiple myeloma. *Am J Hematol* 1985; **20**: 25-29
34 **Barth C**, Bosse A, Andus T. Severe acute cholestatic hepatitis by infiltration of monoclonal plasma cells in multiple myeloma. *Z Gastroenterol* 2005; **43**: 1129-1132
35 **Dubois A**, Dauzat M, Pignodel C, Pomier-Layrargues G, Marty-Double C, Lopez FM, Janbon C. Portal hypertension in lymphoproliferative and myeloproliferative disorders: hemodynamic and histological correlations. *Hepatology* 1993; **17**: 246-250
36 **Alvarez-Larran A**, Abraldes JG, Cervantes F, Hernandez-Guerra M, Vizzutti F, Miquel R, Gilabert R, Giusti M, Garcia-Pagan JC, Bosch J. Portal hypertension secondary

to myelofibrosis: a study of three cases. *Am J Gastroenterol* 2005; **100**: 2355-2358
37 **Wanless IR**, Peterson P, Das A, Boitnott JK, Moore GW, Bernier V. Hepatic vascular disease and portal hypertension in polycythemia vera and agnogenic myeloid metaplasia: a clinicopathological study of 145 patients examined at autopsy. *Hepatology* 1990; **12**: 1166-1174
38 **Pereira A**, Bruguera M, Cervantes F, Rozman C. Liver involvement at diagnosis of primary myelofibrosis: a clinicopathological study of twenty-two cases. *Eur J Haematol* 1988; **40**: 355-361
39 **Valla D**, Casadevall N, Lacombe C, Varet B, Goldwasser E, Franco D, Maillard JN, Pariente EA, Leporrier M, Rueff B. Primary myeloproliferative disorder and hepatic vein thrombosis. A prospective study of erythroid colony formation in vitro in 20 patients with Budd-Chiari syndrome. *Ann Intern Med* 1985; **103**: 329-334
40 **Cervantes F**, Rozman C. A multivariate analysis of prognostic factors in chronic myeloid leukemia. *Blood* 1982; **60**: 1298-1304
41 **Ondreyco SM**, Kjeldsberg CR, Fineman RM, Vaninetti S, Kushner JP. Monoblastic transformation in chronic myelogenous leukemia: presentation with massive hepatic involvement. *Cancer* 1981; **48**: 957-963
42 **Omata M**, Johnson CS, Tong M, Tatter D. Pathological spectrum of liver diseases in sickle cell disease. *Dig Dis Sci* 1986; **31**: 247-256
43 **Blei AT**, Sznajder JI. The liver in lung diseases. In: Rodés J, Benhaumou JP, Blei AT, Reichen J, Rizzetto M, editors. Textbook of Hepatology, 3rd ed. Oxford: Blackwell Publishing, 2007: 1616-1621
44 **Radford AJ**, Rhodes FA. The association of jaundice with lobar pneumonia in the territory of Papua and New Guinea. *Med J Aust* 1967; **2**: 678-681
45 **Kirby BD**, Snyder KM, Meyer RD, Finegold SM. Legionnaires' disease: clinical features of 24 cases. *Ann Intern Med* 1978; **89**: 297-309
46 **Amory JK**, Rosen H, Sukut C, Wallace F, Saint S. Clinical problem-solving. A jaundiced eye. *N Engl J Med* 2006; **354**: 1516-1520
47 **Colldahl H**. A study of serum enzymes in patients suffering from periods of respiratory insufficiency, especially asthma and emphysema. Preliminary report. *Acta Med Scand* 1960; **166**: 399-400
48 **El-shaboury AH**, Thomas AJ, Williams DA. Serum transaminase activity in status asthmaticus. *Br Med J* 1964; **1**: 1220-1223
49 **Henrion J**, Minette P, Colin L, Schapira M, Delannoy A, Heller FR. Hypoxic hepatitis caused by acute exacerbation of chronic respiratory failure: a case-controlled, hemodynamic study of 17 consecutive cases. *Hepatology* 1999; **29**: 427-433
50 **Guevara M**, Arroyo V, Rodés J . The liver in urogenital diseases. In: Rodés J, Benhaumou JP, Blei AT, Reichen J, Rizzetto M, editors. Textbook of Hepatology. 3rd ed. Oxford: Blackwell Publishing, 2007: 1653-1661
51 **Chazouillères O**, Housset C. Intrahepatic cholestasis. In: Rodés J, Benhaumou JP, Blei AT, Reichen J, Rizzetto M, editors. Textbook of Hepatology. 3rd ed, Oxford: Blackwell Publishing, 2007: 1481-1500
52 **Kanai S**, Honda T, Uehara T, Matsumoto T. Liver function tests in patients with bacteremia. *J Clin Lab Anal* 2008; **22**: 66-69
53 **Ding Y**, Zhao L, Mei H, Huang ZH, Zhang SL. Alterations of biliary biochemical constituents and cytokines in infantile hepatitis syndrome. *World J Gastroenterol* 2006; **12**: 7038-7041
54 **Narita R**, Murata M, Kihara Y, Abe S, Tabaru A, Yoshikawa I, Otsuki M. Sepsis presenting with severe jaundice. *Am J Gastroenterol* 2001; **96**: 3214-3215
55 **Fang MH,** Ginsberg AL, Dobbins WO 3rd. Marked elevation in serum alkaline phosphatase activity as a manifestation of systemic infection. *Gastroenterology* 1980; **78**: 592-597
56 **Miller DJ**, Keeton DG, Webber BL, Pathol FF, Saunders SJ. Jaundice in severe bacterial infection. *Gastroenterology* 1976; **71**: 94-97
57 **Neale G**, Caughey DE, Mollin DL, Booth CC. Effects of intrahepatic and extrahepatic infection on liver function. *Br Med J* 1966; **1**: 382-387
58 **Funada H**, Matsuda T, Okada Y. Jaundice associated with Pseudomonas aeruginosa bacteremia complicating acute leukemia. *Intern Med* 1995; **34**: 100-103
59 **Bergert H**, Illert T, Friedrich K, Ockert D. Fulminant liver failure following infection by Clostridium perfringens. *Surg Infect* (Larchmt) 2004; **5**: 205-209
60 **El-Newihi HM**, Alamy ME, Reynolds TB. Salmonella hepatitis: analysis of 27 cases and comparison with acute viral hepatitis. *Hepatology* 1996; **24**: 516-519
61 **Gitlin N**. Liver involvement in systemic infection. In: Gitlin N editor. The Liver and Systemic Disease. Hong Kong: Pearson Professional Limited, 1997: 229-236
62 **Kazakoff MA**, Sinusas K, Macchia C. Liver function test abnormalities in early Lyme disease. *Arch Fam Med* 1993; **2**: 409-413
63 **Horowitz HW**, Dworkin B, Forseter G, Nadelman RB, Connolly C, Luciano BB, Nowakowski J, O'Brien TA, Calmann M, Wormser GP. Liver function in early Lyme disease. *Hepatology* 1996; **23**: 1412-1417
64 **Domingo P**, Munoz C, Franquet T, Gurgui M, Sancho F, Vazquez G. Acute Q fever in adult patients: report on 63 sporadic cases in an urban area. *Clin Infect Dis* 1999; **29**: 874-879
65 **Gordon SC**. Bacterial and systemic infections. In: Schiff ER, Sorrell MF, Maddrey WC, editors. Schiff's Diseases of the Liver. 9th ed. Tokyo: Lippincott William & Wilkins, 2003: 1529-1545
66 **Schlossberg D**. Syphilitic hepatitis: a case report and review of the literature. *Am J Gastroenterol* 1987; **82**: 552-553
67 **Reddy KR**, Farnum JB, Thomas E. Acute hepatitis associated with campylobacter colitis. *J Clin Gastroenterol* 1983; **5**: 259-262
68 **Tajiri T**, Tate G, Iwaku T, Takeyama N, Fusama S, Sato S, Kunimura T, Mitsuya T, Morohoshi T. Right pleural effusion in Fitz-Hugh-Curtis syndrome. *Acta Med Okayama* 2006; **60**: 289-294
69 **Cano A**, Fernandez C, Scapa M, Boixeda D, Plaza G. Gonococcal perihepatitis: diagnostic and therapeutic value of laparoscopy. *Am J Gastroenterol* 1984; **79**: 280-282
70 **Soriano V**, Barreiro P, García-Samaniego J, Martín-Carbonero L, Núñez M. Human immunodeficiency virus and the liver. In: Rodés J, Benhaumou JP, Blei AT, Reichen J, Rizzetto M, editors. Textbook of Hepatology. 3rd ed. Oxford: Blackwell Publishing, 2007: 974-987
71 **Sánchez-Tapias JM**. Bacterial, rickettsial and spirochaetal infections. In: Rodés J, Benhaumou JP, Blei AT, Reichen J, Rizzetto M, editors. Textbook of Hepatology. 3rd ed. Oxford: Blackwell Publishing, 2007: 1001-1010
72 **Mert A**, Bilir M, Tabak F, Ozaras R, Ozturk R, Senturk H, Aki H, Seyhan N, Karayel T, Aktuglu Y. Miliary tuberculosis: clinical manifestations, diagnosis and outcome in 38 adults. *Respirology* 2001; **6**: 217-224
73 **Hay RJ**. Fungal infections affecting the liver. In: Rodés J, Benhaumou JP, Blei AT, Reichen J, Rizzetto M, editors. Textbook of Hepatology. 3rd ed. Oxford: Blackwell Publishing, 2007: 1011-1019
74 **Khan FY**, Kamha AA, Alomary IY. Fulminant hepatic failure caused by Salmonella paratyphi A infection. *World J Gastroenterol* 2006; **12**: 5253-5255
75 **Ichai P**, Roque Afonso AM, Sebagh M, Gonzalez ME, Codes L, Azoulay D, Saliba F, Karam V, Dussaix E, Guettier C, Castaing D, Samuel D. Herpes simplex virus-associated acute liver failure: a difficult diagnosis with a poor prognosis. *Liver Transpl* 2005; **11**: 1550-1555
76 **Gruson D**, Hilbert G, Le Bail B, Portel L, Boiron JM, Reiffers J, Gbikpi-Benissan G. Fulminant hepatitis due to herpes simplex virus-type 2 in early phase of bone marrow

transplantation. *Hematol Cell Ther* 1998; **40**: 41-44
77 **Ho JK**, Tha SP, Coupland R, Dalal BI, Bowie WR, Sreenivasan GM, Krajden M, Yoshida EM. Parvovirus B19 in an immunocompetent adult patient with acute liver failure: an underdiagnosed cause of acute non-A-E viral hepatitis. *Can J Gastroenterol* 2005; **19**: 161-162
78 **Wallot MA**, Metzger-Boddien C, Auth M, Kehle J, Enders G, Dirsch O, Fiedler M, Voit T. Acute liver failure associated with Coxsackie virus B2 infection in a neonate. *Eur J Pediatr* 2004; **163**: 116-117
79 **Harma M**, Hockerstedt K, Lautenschlager I. Human herpesvirus-6 and acute liver failure. *Transplantation* 2003; **76**: 536-539
80 **Dits H**, Frans E, Wilmer A, Van Ranst M, Fevery J, Bobbaers H. Varicella-zoster virus infection associated with acute liver failure. *Clin Infect Dis* 1998; **27**: 209-210
81 **Gasperino J**, Yunen J, Guh A, Tanaka KE, Kvetan V, Doyle H. Fulminant liver failure secondary to haemorrhagic dengue in an international traveller. *Liver Int* 2007; **27**: 1148-1151
82 **Grant JP**, Cox CE, Kleinman LM, Maher MM, Pittman MA, Tangrea JA, Brown JH, Gross E, Beazley RM, Jones RS. Serum hepatic enzyme and bilirubin elevations during parenteral nutrition. *Surg Gynecol Obstet* 1977; **145**: 573-580
83 **Lindor KD**, Fleming CR, Abrams A, Hirschkorn MA. Liver function values in adults receiving total parenteral nutrition. *JAMA* 1979; **241**: 2398-2400
84 **Spiliotis JD**, Kalfarentzos F. Total parenteral nutrition--associated liver dysfunction. *Nutrition* 1994; **10**: 255-260
85 **Cavicchi M**, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. *Ann Intern Med* 2000; **132**: 525-532
86 **Koppe SWP**, Buchman AL. Total parenteral nutrition-related liver disease. In Rodés J, Benhaumou JP, Blei AT, Reichen J, Rizzetto M, editors. Textbook of Hepatology. 3rd ed. Oxford: Blackwell Publishing, 2007: 1634-1641
87 **Carithers RL**. Endocrine disorders and the liver. In: Gitlin N, editor. The Liver and Systemic Disease. Hong Kong: Pearson Professional Limited, 1997: 59-72
88 **Fong TL**, McHutchison JG, Reynolds TB. Hyperthyroidism and hepatic dysfunction. A case series analysis. *J Clin Gastroenterol* 1992; **14**: 240-244
89 **Sato T**, Tajiri J, Shimada T, Hiramatsu R, Umeda T. Abnormal blood chemistry data in Cushing's syndrome: comparison with those for fatty liver. *Endocrinol Jpn* 1984; **31**: 705-710
90 **Olsson RG**, Lindgren A, Zettergren L. Liver involvement in Addison's disease. *Am J Gastroenterol* 1990; **85**: 435-438
91 **Boulton R**, Hamilton MI, Dhillon AP, Kinloch JD, Burroughs AK. Subclinical Addison's disease: a cause of persistent abnormalities in transaminase values. *Gastroenterology* 1995; **109**: 1324-1327
92 **Salmela PI**, Sotaniemi EA, Niemi M, Maentausta O. Liver function tests in diabetic patients. *Diabetes Care* 1984; **7**: 248-254
93 **Foster KJ**, Griffith AH, Dewbury K, Price CP, Wright R. Liver disease in patients with diabetes mellitus. *Postgrad Med J* 1980; **56**: 767-772
94 **Hashizume H**, Sato K, Takagi H, Hirokawa T, Kojima A, Sohara N, Kakizaki S, Mochida Y, Shimura T, Sunose Y, Ohwada S, Mori M. Primary liver cancers with nonalcoholic steatohepatitis. *Eur J Gastroenterol Hepatol* 2007; **19**: 827-834
95 **Silverman JF**, O'Brien KF, Long S, Leggett N, Khazanie PG, Pories WJ, Norris HT, Caro JF. Liver pathology in morbidly obese patients with and without diabetes. *Am J Gastroenterol* 1990; **85**: 1349-1355
96 **Marchesini G**, Brizi M, Morselli-Labate AM, Bianchi G, Bugianesi E, McCullough AJ, Forlani G, Melchionda N. Association of nonalcoholic fatty liver disease with insulin resistance. *Am J Med* 1999; **107**: 450-455
97 **Wei Y**, Rector RS, Thyfault JP, Ibdah JA. Nonalcoholic fatty liver disease and mitochondrial dysfunction. *World J Gastroenterol* 2008; **14**: 193-199
98 **Mastoraki A**, Karatzis E, Mastoraki S, Kriaras I, Sfirakis P, Geroulanos S. Postoperative jaundice after cardiac surgery. *Hepatobiliary Pancreat Dis Int* 2007; **6**: 383-387
99 **Schmid M**, Hefti ML, Gattiker R, Kistler HJ, Senning A. Benign postoperative intrahepatic cholestasis. *N Engl J Med* 1965; **272**: 545-50
100 **Chapman RW**, Angus PW. The effect of gastrointestinal diseases on the liver and biliary tract. In: Rodés J, Benhaumou JP, Blei AT, Reichen J, Rizzetto M, editors. Textbook of Hepatology. 3rd ed. Oxford: Blackwell Publishing, 2007: 1622-1633
101 **Peters RL**, Gay T, Reynolds TB. Post-jejunoileal-bypass hepatic disease. Its similarity to alcoholic hepatic disease. *Am J Clin Pathol* 1975; **63**: 318-331
102 **Peters RL**. Patterns of hepatic morphology in jejunoileal bypass patients. *Am J Clin Nutr* 1977; **30**: 53-57
103 **Baraona E**, Julkunen R, Tannenbaum L, Lieber CS. Role of intestinal bacterial overgrowth in ethanol production and metabolism in rats. *Gastroenterology* 1986; **90**: 103-110
104 **Maddrey WC**. Granuloma of the liver. In: Schiff ER, Sorrell MF, Maddrey WC, editors. Schiff's Diseases of the Liver. 9th ed. Tokyo: Lippincott Williams & Wilkins, 2003: 1563-1579
105 **Hawkins PN**. Amyloidosis. In: Rodés J, Benhaumou JP, Blei AT, Reichen J, Rizzetto M, editors. Textbook of Hepatology. 3rd ed. Oxford: Blackwell Publishing, 2007: 1702-1708
106 **Johnston DE**. Special considerations in interpreting liver function tests. *Am Fam Physician* 1999; **59**: 2223-2230

S- Editor Zhong XY **L-Editor** Alpini GD **E-Editor** Ma WH