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EDITORIAL

Liver physiology and liver diseases in the elderly

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Abstract

The liver experiences various changes with aging that could affect clinical characteristics and outcomes in patients with liver diseases. Both liver volume and blood flow decrease significantly with age. These changes and decreased cytochrome P450 activity can affect drug metabolism, increasing susceptibility to drug-induced liver injury. Immune responses against pathogens or neoplastic cells are lower in the elderly, although these individuals may be predisposed to autoimmunity through impairment of dendritic cell maturation and reduction of regulatory T cells. These changes in immune functions could alter the pathogenesis of viral hepatitis and autoimmune liver diseases, as well as the development of hepatocellular carcinoma. Moreover, elderly patients have significantly decreased reserve functions of various organs, reducing their tolerability to treatments for liver diseases. Collectively, aged patients show various changes of the liver and other organs that could affect the clinical characteristics and management of liver diseases in these patients.

Key words: Liver disease; Aging; Physiology; Immunology

Core tip: The morphology and physiology of the liver changes with aging and an understanding of those changes is important for the management of liver diseases. We first summarized the various changes in the liver with aging. We then reviewed the reported characteristics of liver diseases found in the elderly. This kind of information could be increasingly important in the near future, because the proportion of the world's population over 60 years old is increasing, especially in developed countries.

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INTRODUCTION

The proportion of the world's population over 60 years old is increasing, especially in developed countries. Morphology and functions of the liver as well as other organs change with aging. Understanding these changes is important for the management of liver diseases in the elderly. In addition, the pathogenesis of many liver diseases is immune-mediated, and immune systems also change with aging, affecting the clinical picture of liver diseases.

CHANGES IN LIVER MORPHOLOGY AND FUNCTIONS WITH AGING

Morphology of the aged liver and microscopic or molecular characteristics of senescent hepatocytes

In general, liver volume is reduced by 20%-40% in the elderly, with these reductions more marked in women (up to 44% decline) than in men[1]. Microscopically, elderly subjects have elevated numbers of hepatocytes with increased ploidy. Hepatocytes show decreased numbers of

mitochondria but increased volume of individual mitochondria, although functional impairment of mitochondria has not been demonstrated. Hepatocytes in elderly subjects contain denser body compartments, such as secondary lysosomes and lipofuscin, than do hepatocytes in younger subjects[2]. Lipofuscin accumulation has been associated with chronic oxidative stress and a failure to degrade damaged and denatured proteins[3]. Moreover, accumulating evidence suggests that lipofuscin interferes with cellular pathways due to its ability to trap metallic cations and facilitate further free radical formation[4].

Vacuolation of hepatocyte nuclei has been associated with diabetes mellitus and non-alcoholic fatty liver disease. However, vacuolated hepatocyte nuclei were recently shown to be more abundant in senescent hepatocytes expressing p21 or γH(2)AX[5], suggesting they are a marker of hepatocyte senescence. Moreover, increased size of hepatocyte nuclei in nonalcoholic fatty liver disease (NAFLD) has been associated with telomere shortening and p21 upregulation[6], suggesting that increased nuclear size is also a marker of hepatocyte senescence.

Cellular senescence is associated with aberrant activation of oncogenes, and senescent pre-malignant hepatocytes have been found to secrete cytokines and chemokines through interactions with their environment, resulting in immune-mediated clearance of these cells. Impairment of immune surveillance has been associated with the development of hepatocellular carcinoma (HCC)[7]. This scenario could account for the preferential development of HCC in aged patients with chronic liver diseases, irrespective of the etiology of these diseases[8].

Recently, resistin, an adipokine that inhibits phosphorylation of AMP-activated protein kinase and modulates insulin resistance, has been shown to induce senescence-associated β-galactosidase in mouse hepatocytes[9]. Resistin has been shown to act by inhibiting the function of sirtuin 1, one of the 7 members of the sirtuin family of histone deacetylases shown to act as crucial negative regulators during the aging process[9].

Molecular changes during hepatocyte senescence should be clarified in more detail in the near future. The identification of senescence-causing factors may be beneficial in preventing senescence-associated liver diseases.

Blood flow

Liver blood flow is estimated to be decreased by 35%-50% in the elderly, and may be responsible for age-related reductions in liver volume[10].

Hepatic function

Liver function tests: Although interindividual differences have been observed, liver functions are relatively well preserved in elderly individuals. Hepatic enzymes and high-density lipoprotein cholesterol are well maintained, while bilirubin levels may decline with age due to reductions in muscle mass and hemoglobin concentrations[11]. Moreover, age was reported to be associated with modest decreases in albumin and γ-glutamyl transpeptidase concentrations, and increases in bilirubin concentration, after adjustments for sex, alcohol use, and components of the metabolic syndrome, suggesting that liver function may be decreased in these individuals[12].

Alanine aminotransferase (ALT) concentrations have been reported to decrease with age in both men and women, independent of components of the metabolic syndrome. These findings suggest the need to identify an optimal cut-off point for normal ALT in elderly patients[12].

Drug metabolism

Phase I hepatic metabolism (first-pass hepatic uptake) of drugs has been reported to be decreased in the elderly, possibly due to reduced liver volume and hepatic blood flow, leading to a decline in hepatic drug metabolism. Metabolism of drugs with low phase I hepatic metabolism is likely to be impaired mainly by liver volume reduction.

A previous report suggested that drug metabolism is reduced by up to 30% after 70 years of age, and that a reduction in liver cytochrome P450 may also contribute to decreased drug metabolism. Cytochrome P450 activity was shown to be 32% lower in subjects > 70 years than in subjects aged 20-29 years[13].

Liver regeneration

Liver regeneration capacity has been reported to decline with age[14,15]. The mechanisms underlying the reductions in regeneration capability are complex. One of these mechanisms involves a decrease in the concentrations of circulating epidermal growth factor (EGF), with the response of hepatocytes to EGF also reduced due to age-associated loss of EGF receptors or deficits in signaling after EGF binds to its receptor[16]. Another mechanism underlying reduced hepatocyte proliferation capacity may be the inhibition of cyclin-dependent kinases by interaction with the chromatin remodeling protein Bim, which is expressed in aged hepatocytes[17]. Along with reductions in regenerative capacity, telomere length has been reported reduced in aged livers, especially in patients with liver diseases[18].

Immune system

Many liver diseases are mediated by the host immune response. Therefore, changes in immune functions may affect the clinical picture of various liver diseases. Several changes in the immune system have been observed in elderly individuals.

Innate immunity: Most of the immune cells involved in innate immunity, such as monocytes/macrophages and natural killer (NK) cells, show decreased function with aging[19]. Although the percentage and number of $CD56^{bright}$ NK cells gradually decline with age, the percentage and number of $CD56^{dim}$ NK cells progressively increase[20].

In addition, dendritic cells (DCs), which are the most potent antigen-presenting cells, show significant function-

al changes with aging. DCs play pivotal roles in the onset and regulation of adaptive immune responses and control the state of tolerance to self-antigens[21]. Immature DCs promote tolerance through induction of regulatory T cells (Treg), whereas mature DCs stimulate effector T cells. DCs in the elderly show inappropriate maturation induced by infections or tissue injury, which may lead to alterations in the balance between the tolerogenic and immunogenic functions of DCs and instigate the development of autoimmune diseases[22].

Adoptive immunity: T cell number and diversity of repertoire are decreased and T cell expansion, differentiation, and signaling intensity are impaired with aging. The numbers of $CD4^+$ T cells are decreased, while the numbers of $CD8^+$ T cells are increased. The expression of the costimulatory molecule CD28 is decreased on T cells, impairing their ability to proliferate and secrete interleukin-2[23]. Treg function is decreased after age 50 years, which may be associated with the increases in autoimmunity[24].

The numbers of B cell precursors in the bone marrow (pre-B cells), as well as peripheral B cells, decrease with age[25]. In contrast, immunoglobulin concentrations may increase with age[26], but the quantities of specific antibodies and the diversity of the B cell repertoire decrease[27].

In summary, immune responses against foreign antigens and malignant cells seem to be impaired with age because of the reductions in number and functions of most immunocompetent cells. In contrast, the decrease in Tregs and the impairment of DC maturation may result in a predisposition to autoimmunity.

LIVER DISEASES IN THE ELDERLY

The prevalence of some liver diseases increases with aging, and advanced liver disease is observed more often in older than in younger patients. Moreover, various physiological changes associated with aging may affect the pathogenesis of liver diseases. In addition, the decreased reserve capacity of most organs in elderly individuals may impair their ability to manage liver diseases.

Viral hepatitis

Hepatitis A: Acute hepatitis A virus (HAV) infection is usually self-limiting. However, elderly patients with acute HAV infection experience hepatocellular dysfunction with frequent jaundice and coagulopathy, as well as an increased incidence of complications, such as prolonged cholestasis, pancreatitis, and ascites[28]. Higher hospitalization and mortality rates have been reported in elderly patients with HAV. For example, during an outbreak of HAV infection in the United States, 42% of patients aged 70 years or older required hospitalization compared with 3%-20% of adults aged 40-49 years[29]. Age-related differences in outcomes were also reported, with death rates of 0.004% in individuals aged 5-14 years and 2.7% in those older than 49 years[30]. More recent data from the Centers for Disease Control and Prevention (CDC, 2009 Surveillance) also indicate that mortality due to HAV increases with age, with no fatalities reported in patients younger than 34 years of age. The mortality rates have been estimated to be 0.05 per 100000 patients aged 45-54 years, and 0.11 per 100000 patients older than 75 years. Vaccination for hepatitis A should, therefore, be considered for people, especially the elderly, who plan to travel to endemic areas[30].

Hepatitis B: Acute hepatitis B virus (HBV) infection is uncommon in the elderly because the opportunities for HBV infection are estimated to be low in this population. However, hepatitis B and hepatitis C infections have been reported in aged residents of nursing homes[31,32]. Risk factors include sharing bath brushes, non-disposable syringes, and shaving blades, as well as sexual contact. Clinical manifestations of acute HBV infection are similar to those in younger adults. During an outbreak of acute HBV in elderly nursing home residents, most infected patients were asymptomatic, and no patient died or required hospitalization during the outbreak[31]. However, the rate of progression to chronic hepatitis B is higher in elderly than in younger patients. A report on an outbreak of acute HBV infection in a nursing home showed that 59% of patients older than 65 years of age developed chronic infection[31]. This may be due to a decreased immune response to the pathogens.

In chronic HBV infection, the prevalence rates of HBeAg and HBsAg are inversely related to patient age during the natural course of HBV infection. The prevalence rates of HBsAg in Taiwanese men and of HBeAg among HBsAg-positive men older than 60 years of age were reported to be 12.5% and 5.5%, respectively, while prevalence rates in patients aged 30-39 years were 23.8% and 23.3%, respectively[33]. Serum HBV DNA levels were found to vary by country and to be associated with HBeAg or HBV genotype[34]. Older age and male sex, in addition to serum HBV DNA levels, are regarded as risk factors not only for progression to cirrhosis[35], but the development of HCC[36].

Nucleos(t)ide analogs are effective in treating HBV infected patients, with similar efficacy in the elderly as in younger patients[37]. Although interferon-based therapy may also be effective for the treatment of chronic HBV infection, its therapeutic effects are inferior in elderly patients[38].

Hepatitis C: The prevalence of hepatitis C virus (HCV) infection varies by age because HCV infection is transmitted by blood contact, such as blood transfusion (especially before 1992), military service, intravenous drug use, tattoos, hemodialysis, and health care work. In the United States, the prevalence of HCV infection is highest in patients aged 40-49 years (4.3%), whereas those aged 60-69 years and 70 years or older have lower prevalence rates of 0.9% and 1%, respectively[39,40]. A European

study showed that the prevalence of genotype 1 HCV increases with age, being 57% in patients aged < 65 years, 72% in those aged 65-80 years, and 84% in patients older than 80 years of age[41]. Older age at the time of infection, but not duration of infection, has been associated with fibrotic progression[41] and hepatocarcinogenesis[42]. Normal ALT levels are more likely observed in elderly than in younger HCV-infected patients (46% *vs* 10.6%, respectively)[43]. However, older patients often show more fibrosis regardless of serum ALT levels[41]. Moreover, the incidence of hepatocellular carcinoma increases with aging both in hepatitis C[42] and hepatitis B[44] infected patients. Therefore, progression of fibrosis and development of hepatocellular carcinoma should be considered, especially in elderly patients with chronic viral hepatitis.

Powerful regimens have been established for the treatment of chronic HCV infection, including pegylated interferon and ribavirin, have been established. However, adverse effects are observed more often in older patients[45]. The sustained viral response rate has been shown lower in elderly than in younger patients (46% *vs* 69.7%, respectively), perhaps due to the high proportion of elderly patients who stop antiviral therapy due to side effects[46].

Hepatitis E: The prevalence of hepatitis E virus (HEV) infection differs markedly in endemic and non-endemic areas. However, recent reports suggested that exposure to HEV occurs frequently in Western countries. In the United States, 16% of blood donors younger than 60 years of age were positive for anti-HEV IgG, compared with 25.5% of those older than 60 years[47]. Furthermore, 3% of patients with acute liver injury suspected of being drug-induced liver injury were seropositive for anti-HEV IgM. Most patients with serology consistent with acute HEV infection were older than 60 years of age[48].

Autoimmune liver disease

The prevalence rates of autoimmune liver diseases, including autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC), are relatively high in older patients, whereas primary sclerosing cholangitis is more common in those in the third or fourth decade of life[49-51]. However, the results of laboratory tests associated with these autoimmune liver diseases are not associated with age, and treatment strategies are usually identical in older and younger patients.

AIH: Almost 20% of patients develop AIH after 60 years of age, and the disease is frequently progressive and unexpected because ascites and cirrhosis are common manifestations at presentation with few other symptoms[49,52,53]. Most elderly patients respond well to corticosteroid therapy[52]. Rates of treatment failure are lower in older than in younger patients (5% *vs* 24%), and elderly patients have lower rates of fatality from liver failure or need for liver transplantation (5% *vs* 21%)[52,53]. Notably, elderly patients are at risk of treatment-related complications, especially osteopenia and compression fracture[54]. Furthermore, they may have other comorbidities and medication requirements that complicate their management.

PBC: Advancing age has been associated with poor prognosis in patients with PBC, and elderly patients diagnosed with PBC at a young age are likely to show a poor prognosis[55]. In contrast, patients with PBC diagnosed after 65 years of age are less likely to have progressive or advanced disease[56]. Two types of phenotypic expression of PBC were recently reported: the classical asymptomatic onset in middle-late age with mild biochemical activity, and symptomatic onset at a younger age with high biochemical activity[57]. Administration of ursodeoxycholic acid, which is the only recommended therapy for PBC, appears to be safe and has few side effects. Osteoporosis should also be considered, especially in elderly patients.

Alcoholic liver disease: Alcohol consumption is common in the elderly. In a study of individuals in the United Kingdom, 62% of subjects aged 60-92 years were drinkers, with 13% of men and 2% of women being heavy drinkers[58]. Elderly people presenting with alcoholic liver disease (ALD) had more advanced disease than younger patients[59]. Half of the elderly patients who develop cirrhosis die within 1 year of diagnosis[60]. In patients with HCV infection, alcohol drinking was associated with accelerated disease progression[61]. Adverse effects of benzodiazepines as treatment for withdrawal symptoms, such as drowsiness, fatigue, confusion, ataxia, falls and incontinence, are more common with increasing age[62].

NAFLD: NAFLD is a disease predominantly seen in middle-aged to older people. A significant proportion of cryptogenic cirrhosis may be due to the end-stage of NAFLD, and age has been reported to be a risk factor for liver fibrosis and higher mortality rate in patients with NAFLD[63]. Older patients have significantly more risk factors for NAFLD, including hypertension, obesity, diabetes, and hyperlipidemia[64]. A study of 351 consecutive patients in the United Kingdom found that albumin, alanine aminotransferase (ALT), ALT/aspartate aminotransferase ratio, and platelet counts were significantly reduced with advancing age[64]. Thus, aged patients with NAFLD are considered to have advanced liver disease.

Recently, sirtuin 1, a negative regulator of aging, was reported to play key roles in the regulation of lipid and glucose homeostasis[65]. This finding suggested that aging was associated with the development of NAFLD, and that activating sirtuin 1 may be a novel therapeutic strategy for patients with NAFLD. Several molecular characteristics of hepatocyte senescence have been observed in patients with NAFLD, with hepatocyte senescence being closely associated with advanced fibrosis stage and poor clinical outcome[66]. Thus, the development and patho-

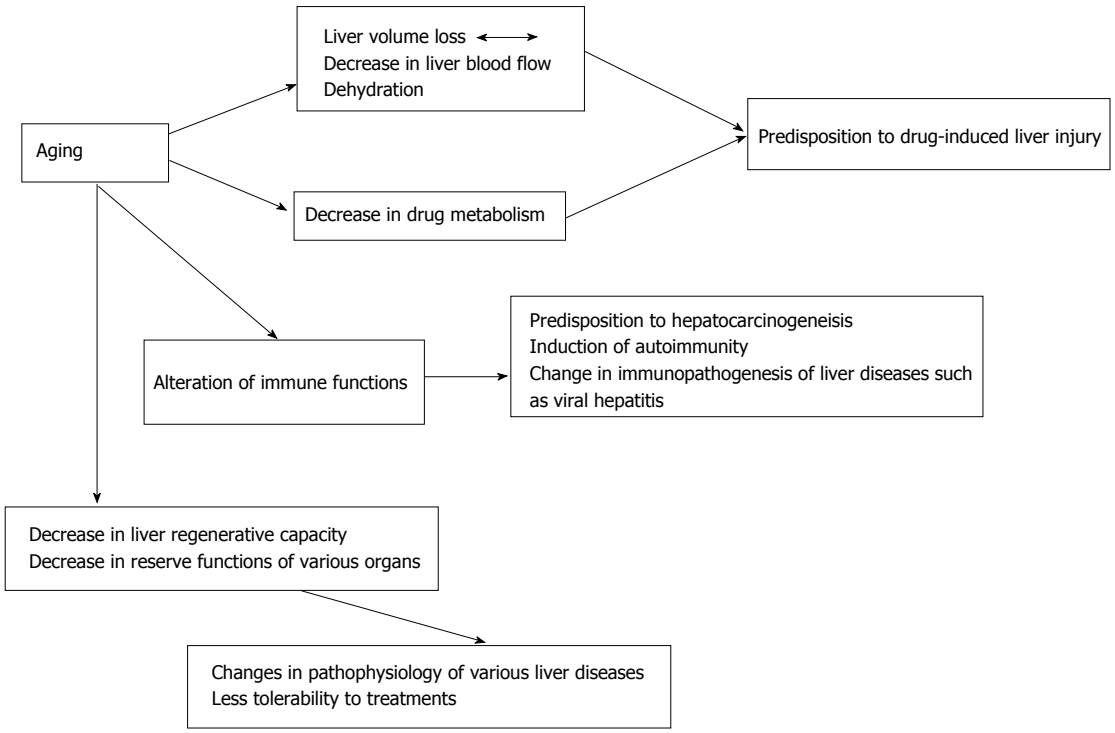

Figure 1 Physiological changes in elderly subjects associated with the development or pathophysiological modification of liver diseases. Aging is associated with decreases in liver volume, blood flow, drug metabolism and regenerative capacity, and alterations in immune functions. Changes due to decreased reserve functions of various organs could affect the clinical characteristics and management of liver diseases in the elderly.

genesis of NAFLD may be closely associated with the aging process.

Drug-induced liver injury: Old age is a risk factor of drug-induced liver injury (DILI) because the elderly are more susceptible to adverse drug reactions[67]. Moreover, patients over 75 years old required significantly longer hospitalization for DILI[68]. In contrast, a recent report suggested that older age is associated with a cholestatic type of liver injury[69], and a study in Japan also showed rates of cholestatic liver injury was higher in patients > 65 than < 65 years of age (46% *vs* 31.6%).

Elderly patients may receive many types of drugs for treatment of comorbid conditions. For example, a Japanese study of patients with DILI showed that elderly patients > 75 years of age were taking significantly more concomitant drugs at the time of liver injury[68]. Other reports from Western countries also suggested greater drug usage among elderly patients. For example, a study of 466 patients in Germany > 70 years of age found that these patients were receiving an average of 3.7 prescribed medicines in addition to 1.4 over-the-counter medications daily[70]. In a prospective study in the Netherlands, 94.2% of elderly patients, mean age 82.3 years, were taking more than one drug, and 73.3% were prescribed four or more drugs[71]. Several pharmacokinetic and pharmacodynamic mechanisms that may predispose a patient on multiple medications to an increased risk of DILI have been proposed[72]. Adverse effects of both the individual drugs and their synergistic interactions must be taken into consideration in elderly patients.

Liver tumor: HCC is more common in elderly patients with liver cirrhosis[73]. Elderly patients were reported to develop HCC even without fibrosis[74], suggesting that aging itself may be a predisposing factor for hepatocarcinogenesis. The impact of viral eradication on HCC prevention was found to be less significant in older than in younger patients chronically infected with HCV, especially in patients at an advanced stage of liver disease[75]. These observations indicate the need for long-term follow-up of elderly patients with chronic HCV infection, even after viral eradication and especially in male patients with liver cirrhosis.

Hepatic resection for HCC can be performed safely and effectively in elderly patients[76]. Regional therapies, such as radiofrequency ablation and transarterial chemoembolization, may also be considered for elderly patients with HCC, if liver function and tumor stage are acceptable[77].

Liver transplantation: The proportion of adult liver transplantation recipients in the United States older than 60 years of age increased from 10% in 1990 to more than 20% by 1999[78]. Some problems remain to be addressed regarding liver transplantation in elderly patients. Increased age has been associated with a poorer survival rate[79,80], although other studies suggested that advanced age alone should not be a contraindication for liver transplantation[81,82]. Among 2141 patients who underwent

Table 1 Clinical characteristics of liver diseases in patients

Liver diseases	Characteristics
Viral hepatitis	
Hepatitis A	Higher hospitalization and mortality rates
Hepatitis B	More likely to progress to chronic hepatitis or cirrhosis
Hepatitis C	More likely to progress fibrosis
	Higher rates of hepatocellular carcinoma development
	Decreased tolerability to treatment
Autoimmune diseases	
Autoimmune hepatitis	Sometimes progressive
Primary biliary cirrhosis	Higher rates of treatment-related complications
	Sometimes progressive
	More likely to have osteoporosis
Alcoholic liver disease	Progressive
Nonalcoholic fatty liver disease	Higher prevalence
	Progressive
Hepatocellular carcinoma	Higher rates of development

retransplantation, more than 10% were over 60 years of age[82]. Being over 60 years of age was not independently associated with an increase in mortality when adjusted for factors that were found to influence survival[82]. Elderly patients may have multiple risk factors, including coronary artery disease or malignancy, and face age-associated quality of life impairments, such as instability, incontinence, immobility, dementia, and polypharmacy[83]. Moreover, aged recipients have a significantly lower quality of life, as assessed by physical functioning, bodily pain, general health, vitality, social functioning, role emotional, and physical component score[84]. Therefore, careful consideration is required in choosing liver transplantation for elderly patients.

CONCLUSION

Aged patients show various changes in the liver, which could affect the clinical characteristics of liver diseases in these patients (Table 1). Decreases in functioning of the liver and other organs as well as alterations in immune functions should be taken into consideration in the management of the liver diseases (Figure 1).

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