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Aging and liver disease

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Abstract

Purpose of review—Aging is a condition in which a person gradually loses the ability to maintain homeostasis, due to structural alteration or dysfunction. Aging is a major risk factor for most chronic diseases. As the liver has a remarkable ability to regenerate, this review assessed the effect of aging on clinical liver disease with references to preclinical models when relevant to pathogenesis.

Recent findings—Aging has been shown to not only enhance vulnerability to acute liver injury but also increase susceptibility of the fibrotic response. Aging is associated with the severity and poor prognosis of various liver diseases including nonalcoholic fatty liver disease, alcoholic liver disease, hepatitis C, and liver transplantation.

Summary—Treatment of older patients with liver disease may require different or longer interventions. Transplantation of an older liver will be less tolerant of subsequent injury. Future studies are needed to understand more about the molecular mechanism of aging and contribute to the development of a noble treatment strategy that can block the progression of aging-induced liver diseases.

Keywords

aging; liver; nonalcoholic steatohepatitis; senescence; transplantation

INTRODUCTION

Aging is a condition in which a person gradually loses the ability to maintain homeostasis, due to structural alteration or dysfunction, and subsequently becomes vulnerable to external stress or damage [1■■]. Aging is a major risk factor for most chronic diseases. Thanks to remarkable socioeconomic development and the advancement of medical care during the past century, the lifespan of humans has been increasing at a steady pace. This has led to a dramatic increase in the elderly population in the world, and the total number of the people

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Conflicts of interest

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aged 65 or more was recorded at 524 million people, equivalent to about 8% of the total global popuplation [2]. It is expected that the elderly population will exceed the 1.5 billion mark or 16% of the world population [2]. In the United States, the population who are 65 years or higher stood at 39.6 million people as of 2009, which is equal to about 13% of the country's total population, and is expected to increase to 72 million people or about 19% of the total population in 2030 [3■]. Among the elderly people, the premature mortality rate due to noninfectious diseases, including ischemic heart disease, cerebrovascular disease, chronic obstructive disability, cancer, and diabetes, is expected to increase, and they are more susceptible to clinical disorders such as visual disturbance, hearing loss, arthritis, and dementia.

Studies have been conducted on the changes in the normal liver and in liver diseases in relation to aging [4]. Aging is associated with gradual alteration of hepatic structure and function as well as various changes in liver cells including hepatic sinusoidal endothelial cells [5]. Aging can also increase the risks for various liver diseases and plays as an adverse prognostic factor, causing an increase in the mortality rate [6,7,8■]. In this review, we provide updated information on the aging-related changes of liver and liver diseases.

AGING AND LIVER VOLUME, BLOOD FLOW, AND FUNCTION

The volume and blood flow of the liver gradually decrease with aging. According to studies using ultrasound, the liver volume decreases by 20–40% as one gets older [4,9–11]. Such changes are related to a decline in the blood flow in the liver, in that those aged 65 years or higher showed an approximately 35% decrease in the blood volume of the liver compared with those aged less than 40 years [10,12]. Meanwhile, the studies that scanned the liver with radioisotopes observed a decrease not in the total liver volume but in the mass of the functional liver cells [13]. Studies have reported mixed results about aging-induced changes in the liver. Humans show a slight decrease in the serum albumin concentration or maintain the normal level in the natural aging process [14]. The neural fat and cholesterol volumes in the liver gradually expand as one gets older, and the blood cholesterol, high-density lipoprotein cholesterol, and neutral fat levels also increase over time. Meanwhile, the metabolism of the low-density lipoprotein cholesterol decreases by 35%. The serum γ-glutamyltransferase and alkaline phosphatase levels are elevated with aging. Although the serum aminotransferase maintains the normal level, the serum bilirubin is gradually reduced, as humans get older [14].

AGING AND LIVER CELLS

Aging-related changes in liver cells include volume changes, polyploidy (polyploidy nuclei), accumulation of dense bodies (lipofuscin) inside liver cells, a decreased area of smooth endoplasmic reticulum, and a declining number and dysfunction of mitochondria [4]. The volume of the liver cells gradually increases as they approach maturity, but starts to decrease due to aging. Lipofuscins are highly cross-linked undegradable protein aggregates that are formed when proteins damaged and denatured by oxidative stress are not degraded inside the liver cells. Such lipofuscins cause increased generation of reactive oxygen species (ROS) in cells and reduced cell survivability [15■]. As a result of aging, hepatocyte polyploidy

tends to occur more frequently over time, which is accompanied by a decreased number and dysfunction of mitochondria, and results in a decline in the ATP level [16,17]. Also, the area of smooth endoplasmic reticulum is reduced, causing decreased generation of smooth endoplasmic reticulum and reducing the synthesis of microsomal proteins in the liver [4].

Compared with the studies on liver cells, relatively little is known about what kind of effect aging has on liver sinusoidal endothelial cells (LSECs), Kupffer cells, and hepatic stellate cells (HSCs). Some studies suggested that aging negatively influences the function of the liver by causing a substantial morphological change in the sinusoidal vascular system [5]. With old age, the thickness of LSECs is enlarged by 50%, whereas the number and diameter of fenestrations (pores) are reduced [18,19]. Also, aging can result in an increase in von Willebrand factor expression, a decrease in caveolin-1 expression, and increased intracellular adhesion molecule-1 expression in the LSECs [20]. The defenestration of endothelial cells can cause the deposition of lipoprotein-like chylomicron in the liver, negatively influence the effective removal of the substance deposited in excess in the liver, and trigger an autoimmune disease by interfering with the interaction between T lymphocytes and hepatocytes [5,21]. As the endocytosis in the LSECs becomes dysfunctional with old age, the deposition of circulating products in the form of giant molecules outside the liver is augmented, which may subsequently increase the risks for aging-related diseases including diabetes, arteriosclerosis, arthritis, and neurodegenerative disorders [22]. The function of Kupffer cells is to remove antigen–antibody complexes or nanoparticles such as senescent cell fragments in the liver sinusoidal vascular system. With old age, the number and activation level of Kupffer cells are increased [23]. Although the number of desmin-positive HSCs goes up with aging, the number of α-smooth muscle actin (SMA)-positive HSCs is observed to maintain the same level [24]. Meanwhile, a recent study analyzing the lengths of telomeres in 73 donors has reported that aging-induced decrease in the length of telomeres was limited only to the ones in Kupffer cells and HSCs, and the length of telomeres in cholangiocytes and hepatocytes was not reduced [25].

ACUTE LIVER INJURY AND LIVER REGENERATION

The aging-related changes including increased oxidative stress, increased inflammatory response, accelerated cellular senescence, and progressive organ dysfunction significantly affect cellular responses to injury [26■]. Furthermore, aging-associated decline in mitochondrial function has been shown to enhance the vulnerability to injury. Acute liver injury was greater in aged rats compared with younger rats in the acute intraperitoneal ethanol or thioacetamide injection models [27,28]. Aging alters stress-induced expression of heme oxygenase-1 in a cell-specific manner, which may contribute to the diminished stress tolerance observed in older organisms [29]. The DNA damage observed in older animals probably results from the accumulation of endogenous damage with age, perhaps due to insufficient repair, which enhances the injury caused by exposure to the toxic agents [30]. Furthermore, a recent study indicated that age-associated change of CCAAT/enhancer-binding protein (C/EBP) family of proteins causes severe liver injury after carbon tetrachloride (CCl_4) treatments [31■]. Aged mice show increase in repressive histone modifications in livers and subsequent repression of three key regulators of liver functions:

C/EBPα, farnesoid X receptor, and telomere reverse transcriptase. These age-related alterations may lead to an increase in liver injury and apoptosis after CCl_4 treatments [31■].

In the sequenced process of liver injury and regeneration, aging decreases regenerative ability, which significantly delays the restoration of liver function [32]. Liver regeneration might be initiated by several stimuli, including surgical resections and treatments with CCl_4 or mitogens. In contrast to livers of younger animals that proliferate to restore liver homeostasis after these injuries, livers of older animals show a significant reduction in proliferation. Recent studies have provided evidence for the crucial role of epigenetic silencing in the age-dependent inhibition of liver proliferation [33]. Aging causes alterations of several signal-transduction pathways and changes in the expression of C/EBP and chromatin-remodeling proteins [34,35]. Consequently, aging livers accumulate a multiprotein C/EBPα–Brm–HDAC1 complex that occupies and silences elongation factor 2 (E2F)-dependent promoters, reducing the regenerative capacity of livers in older mice [35].

LIVER FIBROSIS

Liver fibrosis is a consequence of the excessive healing response triggered by chronic liver injury [36]. In the end stage of liver fibrosis, cirrhosis, the destruction of the normal architecture and the loss of hepatocytes prevent the liver from its normal synthetic and metabolic function. Aging has been considered as a risk factor for progression of fibrosis in hepatitis C and for poor outcome in alcoholic hepatitis [37,38]. Therefore, it has been suggested that aging increases the susceptibility of liver fibrosis. However, biological mechanisms that explain for this predisposition are not well understood. Aging is generally correlated with increased oxidative stress and reduced tolerance to oxidative damage. However, conflicting results have been reported for liver fibrosis in relation to aging. In a study demonstrating increased liver fibrosis with age after chronic CCl_4 injection, there was no higher level of oxidative stress markers between young and old mice [39]. Meanwhile, an increased inflammatory reaction mainly composed of CD4(+) lymphocytes and macrophages expressing helper T cell type 2 cytokines is the main factor involved in the higher susceptibility to fibrosis with increasing age [39]. A recent study investigated the association of age-dependent liver injury and fibrosis with immune milieu [40■]. This indicated that the fibrogenic response to chronic CCl_4 injury was profoundly greater in the old liver than in younger livers, and moreover that macrophage recruitment and dynamics may be an important component in differential age-associated fibrotic disease [40■]. Another study also provided evidence of the role of epigenetic alteration in relation to aging and fibrotic response to injury. This showed that an aged-like mutation of C/EBPα results in a higher level of fibrosis after chronic treatments with CCl_4 [31■]. Thus, age-related fibrosis is an area of unanswered question and active investigation.

NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (NAFLD) includes steatosis (an accumulation of extra fat in the liver), nonalcoholic steatohepatitis (NASH) accompanied by inflammation resulting from damaged hepatic cells, liver fibrosis, and liver cirrhosis. Generally, the prevalence rate of the NAFLD among adults is estimated to be 15–30% [7,41]. The prevalence rate of the

NAFLD shows an increasing tendency as one gets older [7,42]. According to a Rotterdam study of 2811 elderly people aged more than 65 years, the overall prevalence rate of NAFLD was 35.1% [43]. Also, as the population ages, the NASH fibrosis scores display a significant increase and the prevalence rate of liver fibrosis is also increased [44,45■]. Another study, which compared the elderly group aged more than 65 years and the nonelderly group from 18 to 64 years old, reported that the elderly participants showed a higher NASH prevalence rate than their younger counterparts (56 vs. 72%, $P = 0.02$), and also displayed a higher rate of liver fibrosis [45■].

Insulin resistance, which is known to be a primary cause of the NAFLD, is a major component of the metabolic syndrome, which is often observed in elderly people. Aging, which is accompanied by abdominal obesity and excessive visceral fat, causes insulin resistance and an increased secretion of proinflammatory cytokines and, subsequently, results in the metabolic syndromes and type 2 diabetes [46]. In insulin resistance, the secretion of free fatty acids is boosted because of lipolysis in fatty tissues, whereas the synthesis of neutral fat is intensified in the liver by an increased intake of free fatty acids. Molecular mechanisms for the accumulation of excessive fat in the liver and damage to hepatic cells due to aging include increased ROS formation, DNA damage [47■], activation of p300-C/EBP-dependent neutral fat synthesis [48■], telomere shortening [47■], a decreased autophagy [49], increased M1 macrophage inflammatory responses [49], and activation of nuclear factor-κB pathways [8■,50]. In addition, another recent study reported that patients with NFALD showed a shorter length of telomeres, an enlarged nuclear area, and an increased p21 expression, compared with the control group, and that these liver cell aging markers are correlated with the progression of the NAFLD [47■].

Current treatments for NAFLD are to control body weight by changing lifestyle and improve insulin resistance. If body weight is decreased through a medium level of dietary restrictions and increased body activity by 5–10%, it can reduce the fat accumulated inside the liver by approximately 40% [39]. Also, exercise and diet therapy for the elderly can reduce the fat accumulation in the liver and improve hyperlipidemia, hypertension, and insulin resistance [51,52]. Metformin and thiazolidinediones are insulin sensitizers. Metformin is known to be effective in reducing body weight and improving insulin resistance, but its histological effect of improving necrotic inflammation in the NASH has not been proven. In rare cases, it can cause lactic acidosis. Thiazolidinediones are peroxisome proliferator-activated receptor-γ agonists that are known for their effect to improve insulin resistance of the fat cells and the liver. In NAFLD, thiazolidinediones reduce the fat accumulation in the liver and show some effects in the inflammation phases, but failed to improve liver fibrosis. Also, thiazolidinediones are not recommended to elderly patients with heart failure, as they cause a significant increase in the body weight. The bariatric surgery is recommended for patients who have BMI between higher than 40 kg/m^2 and higher than 35 kg/m^2 with metabolic syndromes or type 2 diabetes [53], and it is known to improve necrotic inflammation and fibrosis in the liver by reducing body weight [54]. Although bariatric surgery causes an increase in the morbidity rate among elderly people compared with their younger counterparts, there is no significant difference in the mortality rate except for those with heart diseases; given this, it can be considered as a selective treatment [55]. Liver

transplantation can be an option for patients with decompensated liver cirrhosis. However, in the elderly patients, careful attention should be paid in consideration of common age-related comorbidities, which has a significant influence on their survival and hospitalization period after liver transplantation.

ALCOHOLIC LIVER DISEASE

Excessive alcohol consumption rate has been on the rise among elderly people because of social isolation, divorce or bereavement with their spouses, or depression. According to the National Surveys on Drug Use and Health released between 2005 and 2006, the rate of at-risk drinking among elderly male people, who consume two drinks per day, accounts for 13%, whereas their female counterparts make up for 8% [56]. In terms of binge drinking, which means five drinks per day, the percentage of elderly male people is 14%, whereas their female counterparts account for 3% [56]. The alcohol metabolism ability of elderly people is reduced over time due to a decreased activation level of alcohol metabolic enzymes and the blood ethanol concentration is elevated owing to a reduced distribution volume of water. In addition, the risks of alcohol toxicity may increase due to alteration of alcohol metabolism by the intake of certain medications [57]. Nicotinamide adenine dinucleotide is formed in the process of ethanol metabolism, which increases the synthesis of fatty acids with neutral fat and suppresses the mitochondrial β-oxidation, leading to a fatty liver. With aging, the function of mitochondria decreases, and if it is accompanied by diabetes or metabolic syndromes, fatty liver will increase. An increased generation of ROS and a weakened oxidation defense mechanism increase oxidative stress, and also the gut leakiness boosts the secretion of tumor necrosis factor (TNF)-α by Kupffer cells, which accelerate the progression from fatty liver to steatohepatitis. Such factors can accelerate the generation of liver cirrhosis by activating the transformation of HSCs into myofibroblasts [57].

The clinical symptoms of alcohol liver disease among the elderly are similar to their younger counterparts, but their prevalence of complications is higher than other age groups [58]. Among patients with alcohol liver disease who are older than 60 years, about 79% suffer complications such as alcohol liver cirrhosis; 40% of patients with alcoholic cirrhosis have alcohol hepatitis and the mortality rate of patients with alcohol hepatitis is 15–25%. Aging is related with a bad prognosis of alcohol hepatitis. Alcohol accelerates the progression of not only chronic hepatitis caused by hepatitis B virus and hepatitis C virus (HCV) but also other liver diseases such as NAFLD and hemochromatosis. For those infected with HCV and hepatitis B virus, alcohol consumption can advance the progression of liver cirrhosis and increase the risks for hepatocellular carcinoma [59–62]. For obese people, alcohol intake elevates the accumulation of excessive fat in the liver and worsens liver damage by an increased secretion of TNF-α and cytochrome P-450 2E1 [58]. Meanwhile, as aging increases the risks for comorbidities, elderly people are often under medication of other drugs. As ethanol and most medicines are metabolized by cytochrome P-450-dependent monooxygenase in the liver, elderly patients with alcohol liver disease have higher risks of hepatoxicity because of the interaction with other drugs [57]. The primary treatment for alcohol liver disease is to stop drinking and provide sufficient nutrients and vitamins. However, the glucocorticoid treatment can be helpful for those

patients with moderate alcohol hepatitis whose Maddrey's discriminant function scores are higher than 32. For those who have a contraindication for steroids, pentoxifylline, a TNF-α inhibitor, can be considered as an alternative treatment.

CHRONIC VIRAL HEPATITIS C

About 170 million people are infected with HCV around the world. The anti-HCV prevalence may vary depending on countries, but the elderly tend to show higher anti-HCV prevalence than young people [63–66]. For the HCV transmission routes, those aged 65 years and higher compared with younger people acquire the infection from blood transfusions or surgery prior to 1990, and the infection through intravenous drug abuse is rare [67,68]. The age of a patient at the time of HCV infection diagnosis has proven to be a risk factor for the progression of liver fibrosis, liver cirrhosis, and hepatocellular carcinoma [37,68,69]. If a patient is more than 40 years old at the time of diagnosis of HCV infection, their progression of liver fibrosis is much faster than those under 40 years old [37], and for those aged more than 65 years, the relative risk of severe liver fibrosis (Metavir stage F2 or higher) is 3.78 times higher than that of those under 65 years old [68].

As elderly people commonly show liver fibrosis, they need antiviral treatments. Meanwhile, as many of them suffer from other medical illnesses, they are not allowed to take antiviral treatments or develop side-effects more frequently from the medication. Therefore, for elderly patients with chronic hepatitis C, the antiviral treatment should be determined in consideration of the progression level of liver fibrosis, the expected lifespan, and comorbidities [70■,71]. Since the first introduction of the interferon-alone treatment, the antiviral treatments for chronic hepatitis C have developed dramatically through the combination therapy of peg-interferon-α and ribavirin to direct-acting antiviral agents such as protease inhibitors and polymerase inhibitors. When the elderly people aged more than 65 years are treated with a combination therapy of peg-interferon-α and ribavirin, their sustained virological response (SVR) is lower than those under 65 years old (genotype 1: 22.9 vs. 47.3%; genotype 2: 65.6 vs. 82.9%), whereas their treatment termination rate is higher due to side-effects (genotype 1: 42.9 vs. 24.1%; genotype 2: 24.4 vs. 10.8%) [72]. It has been reported that the supplementation of vitamin D and vitamin B_{12} increases the SVR [73,74■], and as elderly people have a lack of these vitamins, they need to take the supplements. In 2011, two types of protease inhibitors (boceprevir and telaprevir) were approved as the treatment of hepatitis C genotype 1. If a combination of three agents such as telaprevir, peg-interferon-α, and ribavirin is given to genotype 1 patients, there is no significant difference between those over 60 years and those under 60 years (76.6 vs. 83.9%) [75■]. However, this has its own demerit in that the administration schedules of these agents are complicated and can trigger various side-effects such as myelosuppression and rash. Recently, several new direct-acting antiviral agents such as sofosbuvir, a nucleotide analogue, and daclatasvir, an NS5A replication complex inhibitor, are approved or are in phase III clinical development with high SVR rates [76■,77]. Moreover, all-oral, interferon-free combinations of drugs are expected to cure more than 90% of infections [78]. Therefore, further studies on the efficacy and safety of new regimens among elderly patients with hepatitis C should be conducted in the future.

LIVER TRANSPLANTATION

Liver transplantation is a standard treatment for decompensated end-stage liver disease. At present, 1-year survival rate is approximately 90% and 10-year survival rate may exceed 70% in many indications [79]. As the elderly population has been on the rise due to an extended lifespan, the number of elderly patients with complicated liver cirrhosis has grown during the past 2 decades. Given this, more elderly people need liver transplantation. However, there is a controversy over the efficiency of the liver transplantation in the elderly patients due to a limited supply of donors, a high morbidity and mortality rate after liver transplantation caused by comorbidities, a relatively short residual lifespan, and high expenses. The liver transplantation recipients aged more than 60 years showed lower survival rates (1-year survival rate of 64%, a 5-year survival rate of 59%) compared with those aged between 45 and 60 years [80]. The differences are mainly due to kidney dysfunction accompanying cardiopulmonary diseases. Especially, in the case of patients with hepatitis C, the age of recipients is known as a major predictor of the survival rate after liver transplantation [81]. However, more recent studies reported that clinical outcomes after liver transplantation in the elderly are almost similar to young people, if their individual surgery risks are considered to select the right candidate for liver transplantation [82,83]. One Italian study also claimed that there was no significant difference between those over 63 years old and those under 40 years old, in terms of the survival rate of patients and transplanted livers after transplantation surgery [82]. In other studies, liver transplantation recipients aged over 60 years showed similar results in terms of hospitalization period after liver transplantation, consultations, resurgery rate, and rehospitalization rate compared with those below 60 years old [83]. These results could be obtained when patients with low risks are carefully chosen. According to the analysis data revealed by the United Network for Organ Sharing Database, the ventilator status, diabetes mellitus, HCV, creatinine at least 1.6 mg/dl, and combined recipient and donor age at least 120 years are the most powerful prognosis indicators among the recipients of liver transplantation aged more than 60 years. If the numbers of positive indicators among them are 0, 1, and 2, their 5-year survival rates are recorded at 75, 69, and 58%, respectively. If the number of positive indicators is more than three, their 5-year survival rate was below 50% [84]. Therefore, age cannot be a single exclusion criterion from the liver transplantation, and an individualization strategy, which takes into consideration all risk factors of a recipient, needs to be considered.

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KEY POINTS

- Aging is characterized by cellular senescence and alteration of metabolic pathways. The generation of senescent cells is caused by telomere shortening, DNA damage, epigenetic alteration, oxidative stress, and mitochondrial dysfunction, and can result in multiple aging-associated diseases.
- Aging has been shown to not only enhance vulnerability to acute liver injury but also increase susceptibility of the fibrotic response.
- Aging has a significant impact on the risk and poor prognosis of various liver diseases including NAFLD, alcoholic liver disease, hepatitis C, and liver transplantation.