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EDITORIAL

Liver disease in menopause

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Abstract

There are numerous physiologic and biochemical changes in menopause that can affect the function of the liver and mediate the development of liver disease. Menopause represents a state of growing estrogen deficiency, and this loss of estrogen in the setting of physiologic aging increases the likelihood of mitochondrial dysfunction, cellular senescence, declining immune responses to injury, and disarray in the balance between antioxidant formation and oxidative stress. The sum effect of these changes can contribute to increased susceptibility to development of significant liver pathology, particularly nonalcoholic fatty liver disease and hepatocellular carcinoma, as well as accelerated progression of fibrosis in liver diseases, as has been particularly demonstrated in hepatitis C virus liver disease. Recognition of the unique nature of these mediating factors should raise suspicion for liver disease in perimenopausal and menopausal women and offer an opportunity for implementation of aggressive treatment measures so as to avoid progression of liver disease to cirrhosis, liver cancer and liver failure.

Key words: Liver disease; Menopause; Aging

Core tip: There is an interplay of hormonal issues and aging that create a unique path for development of liver disease in menopausal women. Reviewed in this article are the expected liver-related physiologic and biochemical features of menopause and the impact of menopause on the natural history of liver disease. The impact of an understanding of how menopause mediates liver disease is important as there are growing numbers of menopausal women worldwide.

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INTRODUCTION

Chronic liver disease and cirrhosis impose a significant burden on worldwide health. Representing the 12th leading cause of death worldwide, cirrhosis resulted in the death of one million people in 2010, which was 33% more than the number of persons worldwide

Table 1 Benefits of estrogen in liver disease

Inhibition of fibrogenesis
Protection of mitochondrial structure and function
Inhibition of cellular senescence
Increase in innate immunity
Promotion of antioxidant effects

who died of cirrhosis in 1990[1]. Similarly, in the United States, chronic liver disease and cirrhosis represent the 12th leading cause of death with approximately 30000 lives lost each year[2]. More notably, the rate of liver-related death increases among those of older age, with chronic liver disease and cirrhosis representing the fourth leading cause of death in persons aged 45 to 54 years and representing the seventh leading cause of death in persons aged 55 to 64 years. Thus, with increasing age there appears to be an increasing burden of liver disease, and this has been demonstrated in both men and women[3].

For women, issues regarding liver disease are unique in that both age and hormonal factors influence the development and progression of various liver diseases, and it has been demonstrated that this interplay of factors negatively affects the course of liver-related health in postmenopausal women. The average age of natural menopause in the western world is 51 years, and increasingly larger numbers of women are approaching menopause. About 6000 women in the United States reach menopause each day, and it has been estimated that by 2020, more than 50 million women in the United States will be older than age 51 years, the majority of whom will either have fully transitioned to or be in the midst of transitioning into menopause[4]. Worldwide estimates demonstrated that in 1998, more than 477 million women were postmenopausal, and it is estimated that by 2025, 1.1 billion women worldwide will be postmenopausal[5]. Thus, it is becoming increasingly important that the natural history and management of chronic liver disease are understood in the unique context of how they are mediated by menopause.

THE LIVER IN MENOPAUSE

Menopause physiology

Menopause is a gradual process of reproductive aging involving a sequence of hormonal changes over several years that culminates in the cessation of ovarian follicular activity and menstrual cycles. The changes that ensue involve an early follicular phase in the late reproductive years with increased levels of follicle stimulating hormone (FSH) and a decline in levels of inhibin B, a glycoprotein that suppresses FSH and occurs as a result of a decrease in the number of ovarian follicles[6,7]. During this time, estrogen levels are preserved. However, as the menopausal transition unfolds, FSH levels remain high, but estrogen levels begin to fluctuate and eventually decline as the permanent cessation of menses that defines menopause ensues. In the premenopausal state, 17β-estradiol is the predominant and most potent form of estrogen[8]. In the postmenopausal state, estrone, a much weaker form of estrogen, predominates and is produced *via* conversion of androstenedione in adipose tissue and in the liver. In menopause, the interplay of reductions in estrogen levels along with biochemical effects of the aging process foster an environment that increases the propensity for damage within the liver.

Physiologic significance of estrogen

Estrogen exhibits a number of beneficial roles in the body, as it has been shown to promote coagulation, aid in maintaining proper fluid balance, and foster increases in high density lipoproteins and decreases in low density lipoproteins that lead to favorable lipid profiles. Likewise, estrogen exerts a number of liver-related benefits (Table 1). Within the liver, estrogen inhibits proliferation of stellate cells and fibrogenesis. Important steps in the development of fibrosis in the liver include activation of stellate cells, which transform into myofibroblast-like cells, and these cells then proliferate and express α smooth muscle actin (α-SMA)[9]. They synthesize large amounts of extracellular matrix components such as type Ⅰ collagen, type Ⅲ collagen, type Ⅳ collagen, laminin, fibronectin and proteoglycans. In rat models in which hepatic fibrosis was induced with dimethylnitrosamine, treatment with estradiol led to reduced expression of type Ⅰ procollagen as well as reduced deposition of type Ⅰ and type Ⅲ collagens, reduced expression of α-SMA and reduced stellate cell proliferation[10,11].

Estrogen has been shown to regulate the structure and function of mitochondria, particularly in tissues that have a high energy demand. Mitochondria have an important role in ATP production, cell metabolism and apoptosis, and homeostasis of reactive oxygen species (ROS) as well as hepatocyte metabolism of glucose, lipids, and proteins[12]. Dysfunction of mitochondria can lead to disruption of normal cell function and cell membrane permeability and cell senescence, the permanent arrest of cell growth. This process contributes to aging of tissues. Data have shown that estrogen receptors (ERs) and estrogen binding proteins are located within the mitochondria of many cell types, including the liver[13]. Estrogen mediates the structure and function of mitochondria *via* transcription of mitochondrial DNA and induction of nuclear DNA-encoded proteins within the mitochondrial respiratory chain (MRC), leading to enhanced MRC activity with subsequent increased ATP and superoxide[14]. Further, there are data suggesting that knockout of one ER isoform (ERβ1) prevents estrogen-derived protection against mitochondrial membrane depolarization[15].

Demonstration of the ability of estrogen to protect and enhance the function of mitochondria suggests that estrogen may be able to inhibit cellular senescence induced by mitochondrial damage and thus, in turn, slow down the aging process in tissues. This further suggests that the reduction of estrogen as seen in menopause may promote mitochondrial dysfunction, cellular senescence, and tissue aging.

Expected morphologic features of the menopausal liver

There are a number of morphologic changes that occur within the liver as it ages, and thus, such features would be expected to evolve within the liver in menopause. Such changes include reductions in liver blood flow and volume as well as changes in the capacity for liver regeneration. Data have shown that liver volume, blood flow and function decrease approximately 1% per year after age 40 to 50 years[16]. Overall, liver volume decreases by 20% to 40% by the time persons reach elderly age, and this reduction is noted to be more marked in women[17]. Blood flow is reduced by 35% to 50% in the elderly and may contribute to the reduced liver volume that is seen with increasing age[18].

Immunosenescence

Liver injury is mediated in part by the host immune response, and gender and aging influence the role of innate and adoptive immunity in liver disease. Data have shown that female cells show a 10-fold greater expression of the induction of genes associated with toll-like receptor pathways and antiviral type I interferon responses, leading to an increase in the host detection of viral and bacterial nucleic acids[19]. The number and activity of cells of innate immunity, including dendritic cells, monocytes and macrophages are higher in females compared to males[20]. Likewise, the humoral and cellular immune responses to antigens are stronger in females than in males. Women have higher $CD3^+$ and $CD4^+$ cell counts and higher inflammatory helper T-cell type 1 responses than men[21,22]. They also have greater cytotoxic T cell activity and greater upregulation of antiviral and proinflammatory genes than men. It has been observed that these gender differences in components of the immune response are related to the binding of sex steroids, including estradiol, to specific receptors and the subsequent alteration of cell signaling pathways and production of cytokines and chemokines[23]. As the body ages, monocytes, macrophages and dendritic cells have decreased function, and the number and function of T cells also declines[17]. Thus, despite the hormonally-mediated immune advantage that women may have over men in adaptation to injury, this advantage may decline in menopause. As an example, data have shown decreasing $CD4^+$ cells and B lymphocytes as well as declining cytotoxic activity of natural killer cells in menopause[24]. Levels of inflammatory cytokines and interleukins increases, thus creating the inflammatory state associated with menopause[25].

Antioxidants and oxidative stress

Antioxidant enzymes such as superoxide dismutase (SOD) and glutathione S-transferases are important in eliminating ROS and protecting cells against insults from toxic substances and oxidative stress[26,27]. These antioxidants decrease in the liver with aging, thus raising the susceptibility to liver damage. There are decreases in Na^+K^+ATPase and Ca^{2+}ATPase functions in the aging liver as well, and this can negatively alter signal transduction pathways and cell functions, leading to increased lipid peroxidation and fostering a predisposition to liver disorders[28]. Aging livers have been shown to have increases in lipofuscin, which is considered as an end product of increases in lipid peroxidation, thus providing further proof of the aberrant balance of antioxidants and oxidative stress seen in the aging liver[29]. Rat models have shown that the administration of estradiol to aged rats can restore to normal function the otherwise age-related decline in the activity of antioxidant enzymes and membrane-linked ATPases and can lower lipid peroxidation and lipofuscin content in the aged liver[30]. At higher concentrations, such as in the premenopausal state, estrogen exerts antioxidant effects, but at lower concentrations and particularly when containing a catechol, estrogen exhibits pro-oxidant effects, contributing to breaks in genetic material and oxidation of bases, and increasing oxidative stress in the body[8].

LIVER DISEASES IN MENOPAUSE

Hepatitis C

Natural history studies on hepatitis C virus (HCV) disease have demonstrated slower fibrosis progression in women compared to men. Fibrosis progression does not appear to be linear with advancing age, and hormonal differences may mediate the effect of gender on fibrosis progression. Di Martino *et al*[31] demonstrated that among HCV-infected women, higher rates of fibrosis progression occur in postmenopausal women compared to premenopausal women, and this rate of fibrosis progression is higher in postmenopausal women who are not on hormone therapy (HT) compared to postmenopausal women who are on HT[31]. To further underscore the potential beneficial effect of estrogen, it was also shown that fibrosis progression toward advanced liver disease occurs at a higher rate among nulliparous women compared to women who have had at least one pregnancy. Additional data underscore that menopause is associated with higher rates of advanced fibrosis, and the presence of HT in menopause appears to be associated with a lower level of fibrosis[32]. Concurrent steatosis is also seen more frequently in postmenopausal women infected with HCV compared to premenopausal women with

HCV, and the concurrent presence of steatosis is also associated with higher stages of fibrosis.

Menopause has also been demonstrated to have a negative effect on outcomes in the management of HCV liver disease. Recent data have shown that HCV-infected postmenopausal women, particularly nulliparous postmenopausal women, have been less likely to achieve sustained virologic response (SVR) following treatment with pegylated interferon and ribavirin[33]. In these data, a longer duration of menopause (greater than five years) was associated with more severe fibrosis, whereas past pregnancies and HT were not associated with fibrosis severity. Menopause was also associated with higher necroinflammatory activity and higher rates of steatosis compared to that seen in premenopausal women. Potentially identifiable reasons for this were demonstrated through differences in cytokine levels seen in postmenopausal women compared to premenopausal women. Higher levels of TNF-α and IL-6 are seen in postmenopausal women compared to premenopausal women, and higher levels of IL-6 are associated with higher levels of necroinflammatory activity and more severe fibrosis[33,34]. Levels of these cytokines are upregulated in HCV infection and may negatively influence the response to HCV treatment with pegylated interferon and ribavirin. Presently, newer, non-interferon based therapies are available for HCV liver disease. Although data do not exist currently on whether there is any impact of menopause on these rates of response to such treatment, the overall impact may not be as significant as with interferon-based therapies given the overall markedly improved SVRs with these newer therapies.

Gender-specific data on post-transplant outcomes in patients transplanted for HCV liver disease suggest potential concerns regarding the possible effect of menopause and its interplay with age on graft and patient survival following liver transplantation. Belli *et al*[35] were able to demonstrate in a multicenter study that female sex is an independent factor in progression to severe fibrosis in recurrent HCV disease post transplant. Furthermore, in approximately 90% of cases, severe fibrosis progression occurred within five years post transplant in female patients who were allocated older donor (greater than age 60 years) livers, whereas similarly older donor livers allocated to men led to severe fibrosis progression in less than 50% of those male recipients. Whereas this study did not specifically assess the impact of menopausal status on such outcomes, most women in this study were postmenopausal. Lai *et al*[36] provided later data that similarly demonstrated female sex as an independent predictor of severe fibrosis in liver allografts of and increased mortality of patients with recurrent HCV liver disease post-transplantation. Compared to male recipients, women had a 33% increased risk of developing graft failure.

Nonalcoholic fatty liver disease

Recognized as the most common chronic liver disease in the Western world, the median prevalence of nonalcoholic fatty liver disease (NAFLD) in the general population is about 20%, and various factors have been associated with an increased likelihood of developing NAFLD, including obesity, diabetes mellitus, and dyslipidemia[37]. Emerging data suggest that postmenopausal women may be uniquely at risk for NAFLD. Although data have reported a higher incidence of NAFLD in men compared to women, there are observations of persistent increases in the incidence of NAFLD in women beyond middle age, whereas such continued increases in NAFLD incidence are not demonstrated in men[38-40]. Postmenopausal women are clearly at increased risk for the development of the metabolic syndrome compared to premenopausal women, and this is due to multiple changes occurring in menopause, including decreased energy expenditures with development of increased visceral fat, increased weight gain, and increases in triglycerides and cholesterol[41]. Newer data have demonstrated that whereas men with NAFLD have greater severity of hepatic fibrosis than premenopausal women, the severity of hepatic fibrosis in postmenopausal women is similar to that of men, and this effect has been observed even in nonobese postmenopausal women[42,43]. Similar to what has been demonstrated with HCV liver disease, it is believed that such increase in the likelihood of worsening hepatic fibrosis is related to estrogen loss in the postmenopausal state.

Yet, there are still important age-related factors that influence the progression of NAFLD, factors that postmenopausal women would be exposed to given their older age. Features associated with hepatocyte senescence, including telomere shortening and increased expression of p21, are seen in NAFLD, and the increased expression of p21 has been associated with increased levels of fibrosis in NAFLD patients[44]. Murine models demonstrated increased levels of pro-inflammatory cytokines, TNF and monocyte chemoattractant protein 1 in older mice fed high fat diets compared to younger mice given high fat diets, and significant steatohepatitis was observed only in these older mice[45]. Additionally, with aging, increased accumulation of fat is seen in many non-adipose tissues, including the liver[46]. This accumulation of fat in the liver is linked to insulin resistance and increased levels of cytokines, including TNF-α and IL-1, which contribute to oxidative stress and mediate the inflammatory response seen with obesity[47].

Hepatocellular carcinoma

The incidence of hepatocellular carcinoma (HCC) increases with older age, and it occurs in men two to three times more frequently than in women. Recent data from the Surveillance, Epidemiology, and End

Results database have demonstrated that women with HCC have a higher rate of overall survival than men regardless of age, race, stage of HCC, or treatment[48]. Women between the ages of 18 years and 64 years were noted to have longer survival than men of the same age, and the largest difference in survival was noted in women aged 18 years to 44 years. Furthermore, this gender-based disparity in survival in HCC patients disappeared in patients older than 65 years of age. Such gender disparity seen in the development of and survival in HCC is thought to be mediated by estrogen, and these epidemiologic data further suggest that menopausal status may mediate outcomes in HCC. Shimizu *et al*[49] demonstrated that decreased levels of hepatic ERs are associated with development of HCC and that ER levels were correlated with levels of the antioxidant, copper zinc superoxide dismutase (CuZn-SOD), and inversely proportional to the lipid peroxidation product, malondialdehyde. In addition, it was demonstrated that hepatic ER levels were significantly higher in normal livers of premenopausal women compared to hepatic ER levels in postmenopausal women and in cirrhotic patients that either had or did not have HCC. Furthermore, hepatic ER levels were higher in women with cirrhosis than in men with cirrhosis. Other data have shown in murine models that estrogen can suppress production of the inflammatory cytokine interleukin-6 (IL-6) and thus inhibit formation of diethylnitrosamine (DEN)-induced hepatocarcinogenesis[50]. Additional data have also demonstrated that the ER-α protein is downregulated in 60% of cases of HCC in women, and it is believed that activation of the p53/microRNA-18a pathway may promote the upregulation of microRNA-18a that leads to ER-α downregulation and cell proliferation in HCC in women[51,52]. Whereas this mechanism is purported as an explanation for why women develop HCC, further studies will be needed to determine if age mediates this mechanism.

LIVER DISEASE MANAGEMENT IN MENOPAUSE

Data have clearly shown unique issues in the development and natural history of liver disease in menopause. As there is ongoing concern about the progression of liver injury with liver disease in the menopausal state, this also raises concern about the possible need for specialized approaches to liver disease management among women with chronic liver disease who are in menopause or approaching menopause. Previous therapy for HCV liver disease, namely pegylated interferon, carried a substantial side effect profile, and thus, recommendations often suggested consideration for use of pegylated interferon in the setting of patients with more advanced levels of fibrosis[53]. Historically, many HCV-infected patients waited until achieving this level of fibrosis before consideration for treatment. Concern regarding a more accelerated progression of fibrosis in postmenopausal women with HCV liver disease suggests a need for consideration for a more aggressive treatment approach in women, particularly among those who are peri-menopausal or in their younger years of menopause, so as to avoid accelerated progression toward advanced HCV liver disease. Presently, newer HCV treatments, including sofosbuvir, simeprevir, sofosbuvir/ledipasvir, and paritaprevir/ritonavir/ombitasvir/dasabuvir, have minimal side effect profiles, and thus, issues regarding timing of HCV treatment are no longer influenced by concerns about side effects. As these drugs are relatively new and markedly superior in the ability to eradicate HCV infection, there are no data regarding whether there is a reduced likelihood of response to treatment in menopause as has previously been demonstrated in interferon-based treatment. However, there should continue to be concern about ensuring that HCV infection is aggressively managed in all populations and particularly in women who are at risk for acceleration of the severity of HCV liver disease.

Therapy for NAFLD centers on control of the underlying metabolic features associated with NAFLD, including obesity, diabetes mellitus, hypertension and dyslipidemia. As the incidence and severity of NAFLD is increased among older women, particularly in those who have achieved menopause, these observations raise concern about the potential need for a heightened emphasis on weight loss and control of other associated metabolic factors in women who are peri-menopausal and in their early years of menopause so as to hopefully avoid development of advanced fatty liver disease in their older years of life.

More broadly, the influence of estrogen on the progression of liver disease raises query about whether HT may be beneficial in liver disease. HT has been shown to improve a number of clinical conditions associated with menopause, including osteoporosis, vasomotor symptoms, and atherosclerosis. Concern about the negative effects of HT on cardiovascular health were raised in the 2002 Women's Health Initiative trial, which demonstrated an increased risk in the development of heart disease[54]. Secondary analysis of data from this trial led to discovery that there was no increased incidence of heart disease in women on HT between ages 50 and 59 years and among those who were within 10 years of menopause[55]. As menopause ensues and estrogen becomes more deficient, there is decreased activity of estrogen receptors[8]. Further, with aging, there is accumulation of mitochondrial DNA mutations and subsequent mitochondrial dysfunction[56]. Such mitochondrial dysfunction can promote cellular senescence, and senescent cells may produce inflammatory cytokines that oppose the response of estrogen to cytokine formation and may alter expression of certain estrogen-regulated genes[57]. These factors

may contribute to the age-dependent function of estrogen that can be beneficial at younger ages but deleterious in older age. Whereas studies have shown an association of HT with slower fibrosis progression in HCV liver disease and in fatty liver disease, further studies are needed to determine the extent of benefits and overall safety of HT in liver disease.

CONCLUSION

The combination of age and hormonal factors uniquely influence the development and progression of liver disease in postmenopausal women. With recognition of the various physiologic and biochemical changes that occur in menopause, there should be a heightened suspicion for possible liver disease and early implementation of therapies to minimize the likelihood of progression to advanced liver disease, liver cancer, and liver-related death.

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