Sex differences in chronic liver disease and benign liver lesions

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Summary

The epidemiology, natural history, and therapeutic responses of chronic liver diseases and liver lesions often vary by sex. In this review, we summarize available clinical and translational data on these aspects of the most common liver conditions encountered in clinical practice, including the potential contributions of sex hormones to the underlying pathophysiology of observed differences. We also highlight areas of notable knowledge gaps and discuss sex disparities in access to liver transplant and potential strategies to address these barriers. Given established sex differences in immune response, drug metabolism, and response to liver-related therapies, emerging clinical trials and epidemiological studies should prioritize dedicated analyses by sex to inform sex-specific approaches to liver-related care.

Keywords: Gender; Liver; Epidemiology; Sex disparities

Received 27 January 2023; received in revised form 23 June 2023; accepted 1 July 2023; available online 1 August 2023

Introduction

The epidemiology, natural history, and therapeutic responses of chronic liver diseases and liver lesions often vary by sex. In this review, we summarize available clinical and translational data on these aspects of the most common liver conditions encountered in clinical practice, including the potential contributions of sex hormones to the underlying pathophysiology of observed differences. We also discuss sex disparities in access to liver transplant and potential strategies to address these barriers. Regarding terminology, the term "women" and "men" in this review will refer to individuals assigned female or male sex at birth, respectively, though dedicated studies within transgender populations are greatly needed, including on the influence of gender-affirming exogenous hormone use on the natural history of chronic liver disease.

Fibrotic diseases

The human liver expresses cellular receptors for several sex hormones, including androgens, oestrogens, and progesterone, with oestrogen being the most widely studied sex hormone with respect to hepatic fibrosis.[1] Oestrogens have a direct inhibitory effect on hepatic stellate cells, which are activated in response to liver injury and subsequently produce collagen.[2,3] Studies in preclinical and animal models have demonstrated the antifibrotic effects of oestrogens through various pathways involving, but not limited to, interleukin (IL)-6 activity, signal transducer and activator of transcription 3 (STAT-3) phosphorylation, transforming growth factor-β, and extracellular signal-regulated kinase.[1] For example, *in vitro* studies using human hepatic stellate cells have demonstrated that increased oestrogen receptor expression reduces transforming growth factor-β production by inhibiting STAT-3 phosphorylation.[4] Increased levels of phosphorylated STAT-3 in hepatocytes and hepatic stellate cells have been associated with increased inflammation, ballooning, and fibrosis.[5]

Interestingly, oestrogen has been shown to play a role in improving liver injury once present by restoring microRNA pathways that regulate hepatic stellate cells.[6] Beyond mediating inflammatory markers and hepatic fibrosis, oestrogen also plays a key role in regulating lipid and glucose homeostasis as further discussed in the non-alcoholic fatty liver disease (NAFLD) section.

Oestrogen's protective effects against liver injury and fibrosis likely account for the higher prevalence of advanced fibrosis in men compared to women for many chronic liver diseases. Likewise, the risk of fibrosis increases following the menopausal transition, with data from women co-infected with HIV/HCV showing an increased risk of fibrosis with reproductive aging, independent of chronologic aging.[7] In the following sections we will review sex differences in the natural history of chronic liver diseases and liver lesions, including disease-specific data on the role of sex hormones in these processes.

NAFLD

NAFLD affects approximately one-third to one-quarter of individuals globally, though prevalence estimates differ by sex and reproductive status[8,9] (Fig. 1). NAFLD prevalence is generally thought to be higher in men, although this finding dissipates when comparing estimates in men and post-

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menopausal women.[10,11] The risk of advanced fibrosis related to non-alcoholic steatohepatitis (NASH) does appear to be greater in women aged over 50 than in men.[9,12,13] Indeed, NASH is now the leading indication for liver transplant in women, and the second most common indication for transplant in men.[14] As noted above, these epidemiologic trends likely relate in large part to the protective effects of oestrogens against hepatic stellate cell activity and subsequent fibrosis.[15] Premature menopause and longer durations of oestrogen deficiency have been shown to increase the risk of advanced NASH fibrosis.[16] In a large case-control study from Europe, oophorectomy in women aged under 50 was associated with a 50% increased risk of NAFLD.[17] Data from cell culture and animal models have established the mechanistic roles of hepatic oestrogen receptors in regulating glucose and lipid homeostasis, as well as hepatic insulin sensitivity in both men and women,[18] which likely contributes to age-related increases in NAFLD prevalence and fibrosis severity across sex.[18] These basic and translational data are also supported by clinical findings of lower NAFLD prevalence among post-menopausal women receiving menopausal hormone therapy (MHT).[19]

Interestingly, while oestrogens have been shown to have a protective effect on liver disease in both male and female models of liver disease, androgens have clear sexually dimorphic effects on the presence and severity of NAFLD, including on histologically confirmed NASH.[20–23] Testosterone is traditionally considered a "male" sex hormone but has well-established sexually dimorphic effects on metabolic health, with higher levels promoting hepatic steatosis, as well as diabetes and dyslipidaemia in women, while opposite effects are apparent in men.[21,23–25] Data supporting these findings in women initially derived from patients with the common endocrinopathy polycystic ovary syndrome (PCOS), a typically hyperandrogenic condition in which over 50% of patients have imaging-confirmed NAFLD, as well as being at higher risk of NASH and advanced NASH fibrosis.[26–29] Though 10% of women with PCOS have androgens in the normal range, the hyperandrogenic PCOS phenotype is associated with prevalent NAFLD.[30,31] Beyond PCOS, higher testosterone levels within the normal range are also associated with increased risk of prevalent NAFLD in women, independent of comprehensive metabolic risk factors, while higher testosterone levels in younger patients without PCOS have also been shown to be independently associated with NASH severity.[21,22] Such findings contrast with the observed increased risk of prevalent NAFLD, as well as increased histologic severity of NASH, associated with lower testosterone levels in men.[20,23] Indeed, testosterone replacement in men improves insulin resistance, lipid profiles, and visceral adiposity, supporting a more direct role of testosterone on metabolic risk factors for NAFLD/NASH.[32,33] Data from sex-specific animal models align with these clinical observations, including sexually dimorphic effects at the level of the liver in response to androgen receptor activity. This includes androgen receptor-mediated increases in hepatic gluconeogenesis, *de novo* lipogenesis, and impaired fatty acid oxidation in men/male animal models with low testosterone

Key points

- The epidemiology and natural history of many chronic liver diseases differs by sex.
- Differences in endogenous sex hormones appear to contribute to less hepatic fibrosis and hepatocellular carcinoma in women, though hormonal contributions across all liver diseases are not consistent.
- Given established sex differences in immune response, drug metabolism, and response to some liver-related therapies, emerging clinical trials must prioritize dedicated analyses by sex.

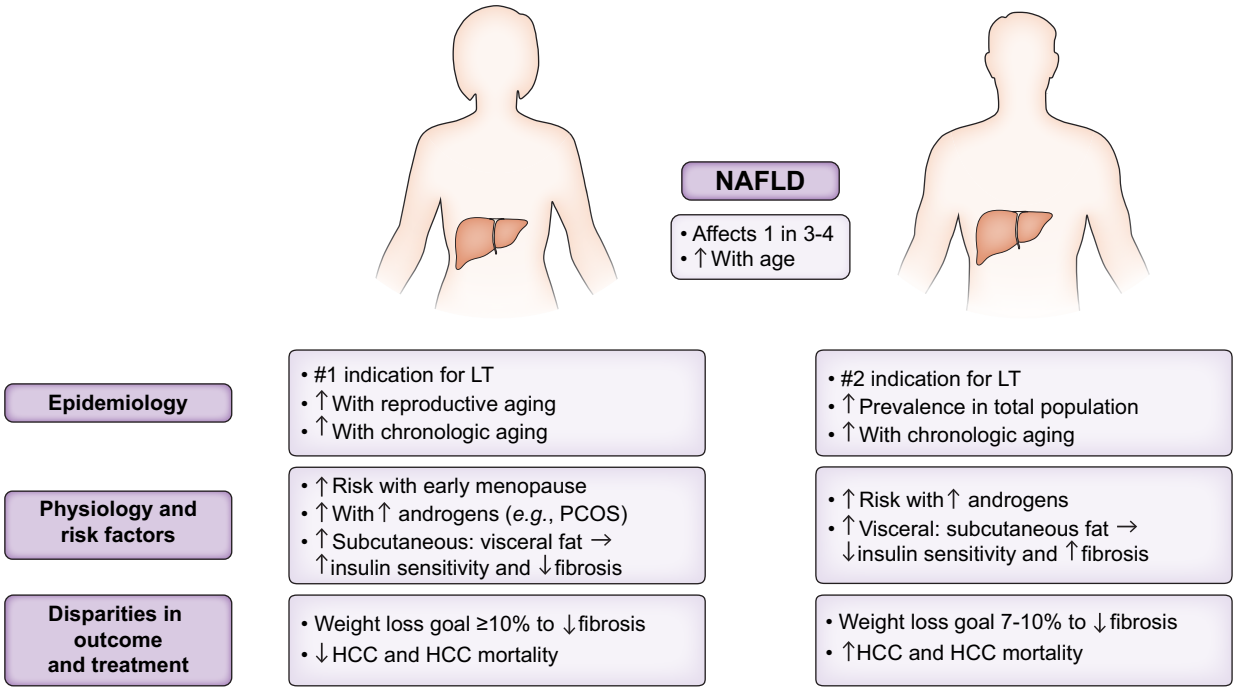

Fig. 1. Sex differences in NAFLD. Left: Characteristics in women. Right: Characteristics in men. HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovarian syndrome.

or impaired androgen receptor activity and in response to high testosterone in women/female animal models.[18]

Taken together, there is a clear need to recognize the relevance of sex- and gender-specific influences on the natural history of NAFLD, and tailor treatment studies accordingly. To date, few trials have evaluated sex-specific responses to treatment interventions, though differences in lifestyle exposures and lifestyle changes appear to differentially affect men and women. For example, the mainstay of NAFLD management is weight loss, with a goal of 7-10% total body weight loss advised to improve NAFLD histology, though women need at least 10% to achieve similar effects.[34] Body composition also differs by sex with women having more subcutaneous fat, less visceral adiposity, and consequently higher insulin sensitivity, with less adipose tissue lipolysis and free fatty acid delivery to the liver. In response to excess dietary sugars and fat, women also tend to have greater insulin sensitivity, less hepatic lipid uptake, and more lipid export out of the liver than men, suggesting a more favourable adaptive response to these dietary insults.[18,35]

Alcohol-associated liver disease

Approximately 26 million people have cirrhosis related to alcohol-associated liver disease (ALD) globally, and the prevalence of those with decompensated liver disease is increasing.[36] Hospital admissions and the burden of ALD have increased over time and to a greater extent in women over the last two decades.[37] In general, women are likely more susceptible to the hepatotoxic effects of alcohol, but the prevalence of ALD is higher in men due to increased rates of consumption (Fig. 2).[38–40] Women do have more accelerated disease progression with ongoing alcohol use than men. For example, there is evidence that it takes 20 years on average for cirrhosis to develop from ALD in women compared to 35 years in men.[41] Further, female sex is an independent risk factor for alcohol-associated hepatitis, progression to cirrhosis, liver-related death, and overall mortality in the setting of ALD.[42,43] Women also die at earlier ages with a higher risk of mortality than men.[41] Women with ALD are also more likely to be de-listed from the liver transplant waitlist than men and less likely to receive a transplant. Importantly, women with ALD are less likely to receive treatment for alcohol use disorder by way of face-to-face visits and medications for relapse prevention.[44]

The reasons for the increased susceptibility to ALD in women are multifactorial. Women have smaller body mass than men which results in less alcohol dilution. Women also have decreased gastric alcohol dehydrogenase (ADH) activity, which is involved in first-pass alcohol metabolism, resulting in higher blood alcohol concentrations per unit alcohol consumed, independent of body mass.[45] Furthermore, chronic alcohol use decreases gastric ADH activity to a greater extent in women than in men, resulting in higher levels of alcohol reaching the liver. Data on hepatic ADH levels are sparse, though one study demonstrated that women also have decreased hepatic ADH activity compared to men.[46] While these data explain increased levels of blood alcohol in women compared to men, it is unclear if this affects hepatic fibrosis.

Oestrogen has been shown to increase the sensitivity of Kupffer cells to lipopolysaccharides, which results in inflammation and toxic byproduct production in preclinical models of ALD.[47,48] The influence of alcohol on sex hormone expression may also play a role. Data from mouse models have shown increased alcohol-induced expression of oestrogen receptors in

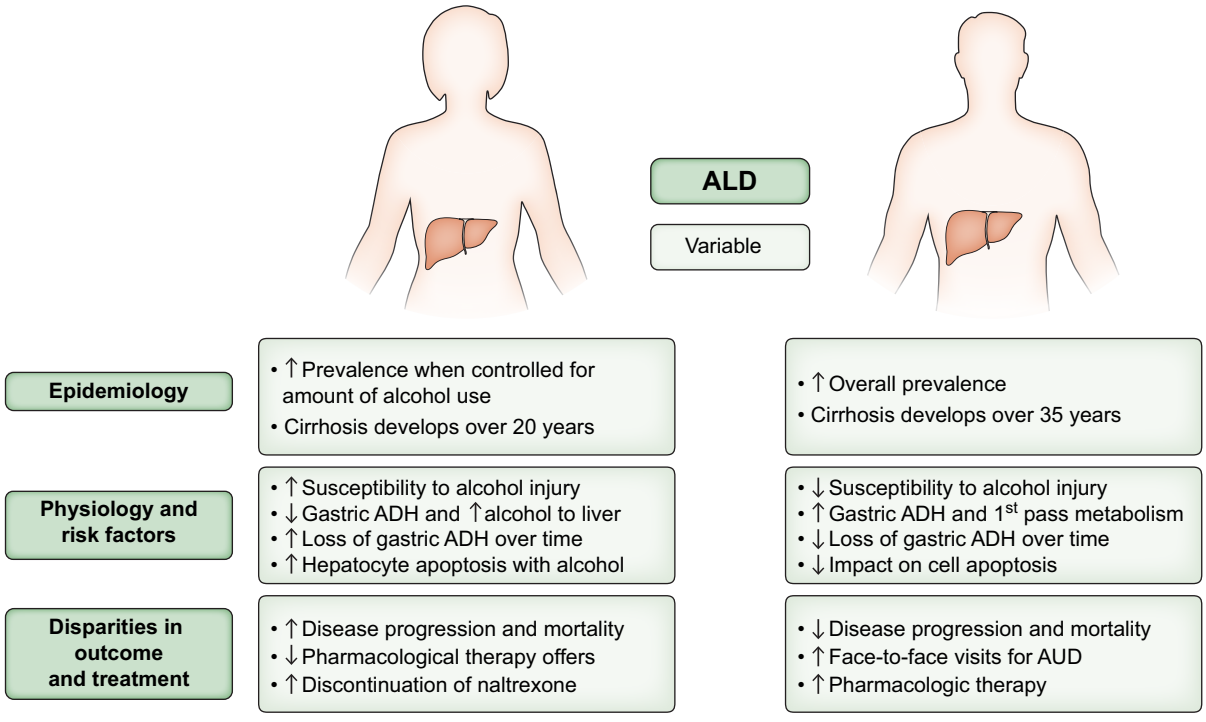

Fig. 2. Sex differences in ALD. Left: Characteristics in women. Right: Characteristics in men. ADH, alcohol dehydrogenase; ALD, alcohol-associated liver disease; AUD, alcohol use disorder.

hepatocytes of male mice.[49] Increased circulating oestrogen levels and hepatic oestrogen receptor expression were associated with improved hepatocyte proliferation in male mice. Alcohol exposure did not significantly alter oestrogen receptor expression in hepatocytes from female mice and hepatocyte apoptosis was more prominent in female mice.[49] Recent data using mouse models showed that histone 3 lysine K4-specific demethylase enzymes known as KDM5B and KDM5C were impacted by alcohol exposure in a sex-dependent manner. These demethylases were shown to downregulate aryl hydrocarbon receptor signalling in hepatic stellate cells in female mice, which promoted stellate cell activation and fibrosis, a phenomenon that was not observed in male mice.[50] These differences may relate to the role of oestrogen in regulating aryl hydrocarbon receptor-dependent gene expression.[51] Data in human tissue are needed to understand whether findings from animal models may contribute to the sex disparities in clinical outcomes observed in ALD.

HBV

The global prevalence of HBV is between 2-7% (Fig. 3). Men are less likely to spontaneously clear HBV infection and are thus more likely to become chronically infected.[52] Male sex is also an independent risk factor for HBV-associated complications including being associated with a 2.5x higher risk of cirrhosis, 3-6x higher risk of hepatocellular carcinoma (HCC), and 1.8x higher risk of death.[53–55] Sex differences in HBV outcomes may relate to interactions of the virus with sex hormones. Androgen activity is increased in the setting of HBV, which stimulates viral transcription, creating a positive feedback loop that results in higher viral replication and oncogenic potential.[56] Higher testosterone levels have been associated with an increased HCC risk in patients infected with HBV.[57] On the contrary, oestrogen is felt to play a synergistic role in the immune response to HBV, leading to improved viral clearance. CD107a expression by natural killer (NK) cells is considered a marker for degranulation, the process by which cytotoxic granules are released to kill a targeted cell. Degranulation of NK cells is crucial in controlling HBV infection. CD107+ intrahepatic NK cells are more prevalent in women than men, to an extent that correlates directly with oestradiol levels.[58] Additionally, oestrogen may hinder HBV transcription by upregulating oestrogen receptors, which interfere with binding of the HBV enhancer.[56] The protective effect of oestrogen in HBV is supported by data demonstrating lower risk of HBV-related complications, and HCC in particular, among post-menopausal women on MHT.[57] Given sex differences in HCC risk, the American Association for the Study of Liver Diseases supports earlier initiation of HCC screening in Asian men with HBV at age 40 years, *vs.* age 50 years for Asian women with vertically acquired HBV.[59] The European Association for the Study of the Liver and the Asian-Pacific Association for the Study of the Liver society guidelines do not provide HCC screening recommendations by sex, but do advise the use of risk calculators, such as the REACH-B or PAGE-B, that include sex as a variable.[60,61]

HCV

The global prevalence of chronic HCV is estimated to be 0.7%, with men affected twice as often as women (Fig. 3).[62] Similar to HBV, women are more likely to spontaneously clear HCV infection. In addition, women with HCV are more likely to achieve sustained virologic responses with antiviral therapy.[63,64] Oestrogen is felt to promote the immune response to HCV. For example, 17 beta-oestradiol has been shown to interfere with the life cycle of HCV through intracellular receptor signalling,

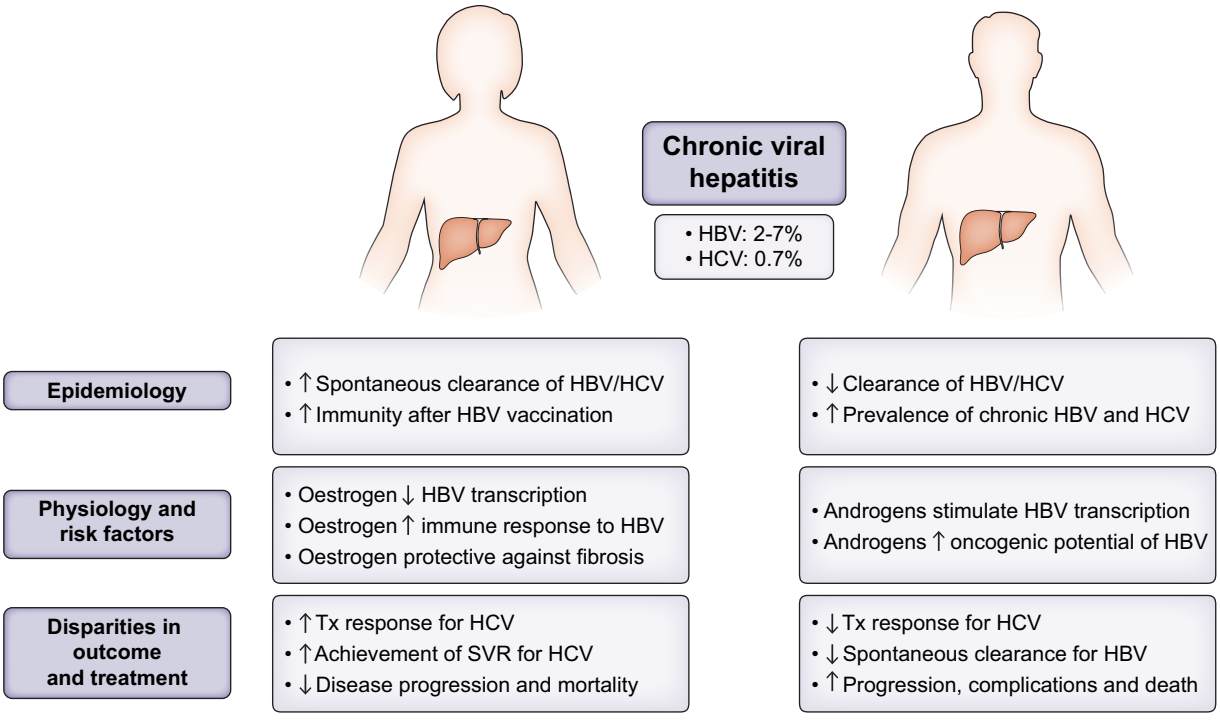

Fig. 3. Sex differences in chronic viral hepatitis B and C. Left: Characteristics in women. Right: Characteristics in men. SVR, sustained virologic response; Tx, treatment.

inhibiting viral production.[65] Further, male sex is an independent risk factor for fibrosis progression in HCV and men develop cirrhosis 10 years earlier than women on average.[66,67] Even after direct-acting antiviral treatment with sustained virologic response, men have higher rates of liver-related mortality and need for transplantation than women.[68] Similar to other aetiologies, oestrogen is known to have a protective effect on HCV fibrosis. Pre-menopausal women with HCV have decreased fibrosis progression compared to men, a difference that is not observed after menopause.[67,69] Decreased fibrosis progression has been demonstrated in post-menopausal women receiving MHT.[70] While oestrogens clearly have a protective effect against hepatic fibrosis, once cirrhosis is present, oestrogen levels have been shown to be higher in both men and women, which likely relates to increased peripheral conversion of androgens to oestrogens in the setting of advanced liver disease.[71–73]

Autoimmune liver diseases

Autoimmune hepatitis

Autoimmune hepatitis (AIH) affects <0.01% of the population, with a female to male ratio of 4 to 1 (Fig. 4).[74] Overall fibrosis progression and risk of cirrhosis are similar by sex.[75,76] However, men typically present at a younger age and may be more likely to have cirrhosis at the time of diagnosis.[75,77] Treatment response and relapse rates are similar.[76,78] However the largest study to date (N = 1,318) identified male sex as an independent predictor of increased mortality or need for liver transplant.[79] Conversely, a study of 238 patients with biopsy-proven AIH found that women had lower overall survival over a 30-40-year follow-up (p = 0.02), but found no differences in the proportion with liver-related death or need for liver transplant.[75] Interestingly, transplant need for AIH has been shown to be predicted by underlying genetic polymorphisms (*e.g.*, human leukocyte antigen [HLA]-DR3, HLA-DR4) rather than sex itself.[78] Women are more likely to have HLA-DR4, while men are more likely to have HLA-DR3. HLA-DR3 is associated with higher rates of disease progression and treatment failure compared to HLA-DR4, however, this is independent of sex.[76,80] After liver transplant, AIH recurs in 25% of transplant recipients with no differences by sex.[81]

The biology underlying the female predominance of AIH is complex, involving epigenetics, sex-chromosome factors, and hormonal influences on innate immunity.[82,83] For example, oestrogen and androgen receptors are expressed on B lymphocytes, whereas CD8+ T lymphocytes, monocytes, neutrophils, and NK cells express oestrogen but not androgen receptors.[84] Interestingly, disease quiescence during pregnancy and post-partum flares have been shown to relate to oestrogen-associated shifts in immunity.[85] Earlier gestational age reflects a more immune suppressive state that enables the body to "tolerate" the growing fetus. Increased circulating oestrogen contributes to a change in T cell profiles from a predominance of type 1 to type 2 T helper cells, which lessens disease activity. Rising oestrogen levels and associated shifts toward immune activity, particularly in the third trimester and post-partum period, result in more predominant type 1 T helper cell activity and increased risk of AIH flares.[85] Testosterone levels are less well studied in AIH, though testosterone reduces type 1 T helper cell activity and may contribute to lower AIH risk in men.[86]

Primary biliary cholangitis

PBC affects 20-40 per 100,000 adults, with a strong female predominance. Though the number of men diagnosed with PBC is increasing, 90% of cases are observed in women[87] (Fig. 4). Of the autoimmune liver diseases, the most robust data on sex differences in presentation and outcomes are available for PBC. In terms of diagnostics, anti-mitochondrial antibody is absent in

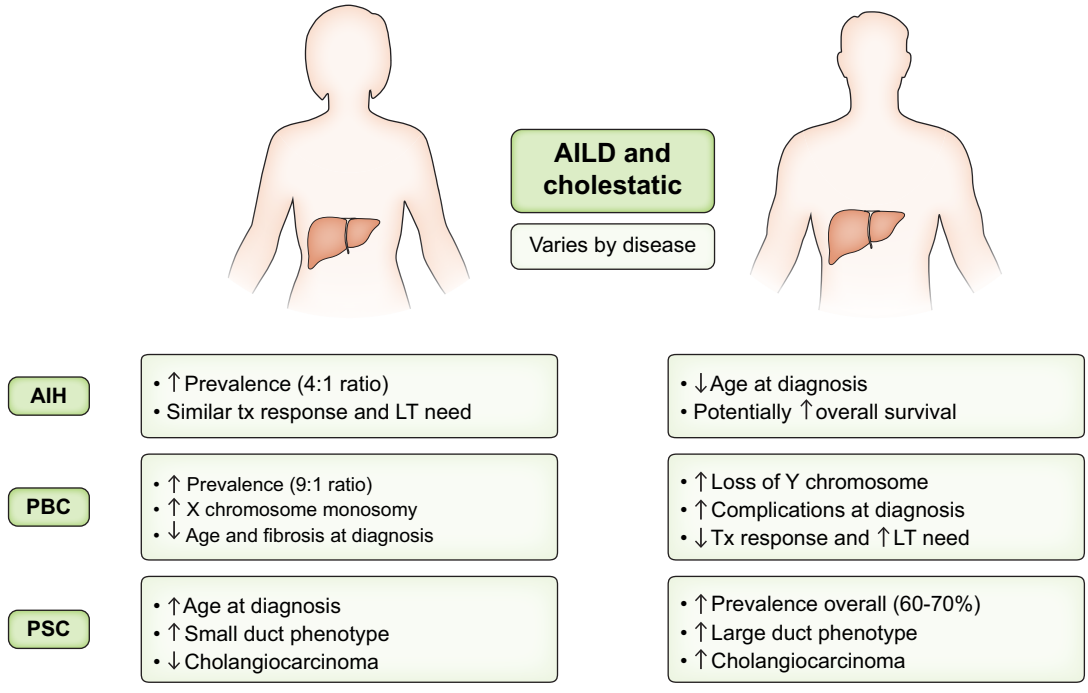

Fig. 4. Sex differences in autoimmune and cholestatic liver diseases. Left: Characteristics in women. Right: Characteristics in men. AILD, autoimmune liver diseases; LT, liver transplant; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; Tx, treatment.

15% of women with PBC while anti-mitochondrial antibody negativity typically excludes a diagnosis of PBC in men.[88] Women are typically younger and more symptomatic than men at diagnosis. Women report more fatigue and pruritis, which may relate to hormonal differences.[89] Pruritis increases with combined hormonal contraceptive pills and during pregnancy,[89] which likely relates to oestrogenic effects on bile acid secretion. Women with PBC are also more likely to have other concomitant autoimmune diseases.[90]

At presentation, men often have higher bilirubin levels and more clinically significant liver disease, including cirrhosis, portal hypertension, and decompensation.[91,92] In terms of treatment, men are less likely to respond to first-line treatment with ursodeoxycholic acid.[93,94] To date, there are no available data regarding sex differences in response to obeticholic acid, a second-line agent. Men with PBC have increased pre-transplant mortality and are at a 3-fold greater risk of HCC.[94] It is recommended to screen for HCC every 6 months regardless of fibrosis stage, while HCC screening is only indicated in women with advanced fibrosis.[87]

Liver transplant for PBC is now primarily reserved for those presenting with decompensated cirrhosis, HCC, and treatment non-responders with progression to advanced disease.[93,95] Male sex is an independent risk factor for liver transplant, likely due to decreased responses to ursodiol and the increased risk of HCC.[94] After liver transplant, Recurrent PBC occurs in 20-30% of patients within the first 10 years of transplant,[87] with no sex differences in recurrence rate.[96,97]

The origins of sex differences in PBC are also multifactorial and include genetic, epigenetic, hormonal, and immune differences. An increased rate of X monosomy has been observed in female patients with PBC.[82] Increased X monosomy in PBC and other autoimmune diseases suggests that haploinsufficiency of genes located on the X chromosome are related to disease pathogenesis. This has been supported by data in males showing that PBC is associated with loss of the Y chromosome in peripheral immune cells.[82]

Further, a preclinical model of PBC has demonstrated different levels of interferon type I and II activity in the livers of female compared to male mice. Interferons are proposed to increase the inflammatory response in the liver and occur more often in female mice due to increased interferon activity.[98] The same research group completed a follow-up experiment where they knocked out the gene responsible for interferon-gamma and found that liver pathology was reduced and sex differences dissipated in the absence of type 1 interferon signalling.[99]

Oestrogen-related signalling of cytokines may promote activity and inflammation.[99] Oestrogen receptors within the biliary epithelium of patients with PBC have been linked to increased inflammation through IL-6-mediated mechanisms that contribute to the progression of autoimmune liver diseases, specifically PBC and AIH.[100] Conversely, testosterone has been shown to reduce cholangiocyte inflammation.[101] Testosterone treatment has been shown to suppress liver inflammation in female mice while testosterone deprivation increased inflammation in male nice via IL-17-mediated pathways.[101] At present, the causal role of either oestrogens or androgens on PBC-specific disease progression in men and women is not clear.

Primary sclerosing cholangitis

The prevalence of primary sclerosing cholangitis (PSC) varies worldwide and ranges from 6-16 per 100,000 adults[102] (Fig. 4). PSC is unique amongst the autoimmune liver diseases in having a male predominance, with 60-70% of cases diagnosed in men.[103,104] Historically the age of onset was considered to be similar in men and women,[96] however more recent data suggest that women tend to be older at diagnosis, and more likely to have late-onset disease.[105,106] Phenotypically, women are more likely to have small duct PSC, which is protective against cholangiocarcinoma risk, while men are more likely to have large duct PSC.[105] Up to 80% of patients with PSC have concurrent inflammatory bowel disease, typically ulcerative colitis, which is associated with large duct PSC and male sex.[107,108] Though smaller studies report similar survival between men and women,[103,109] the largest study to date (N = 7,121) evaluated PSC progression over 30 years of follow-up and found female sex to be protective against liver fibrosis, with women having greater transplant-free survival.[105] Severe complications of PSC, including cholangiocarcinoma and colorectal cancer, are less common in women and likely contribute to sex differences in survival.[105,110] In terms of liver transplant for PSC, 70% of waitlist candidates are men.[111] After transplantation, recurrent PSC occurs in 15-20% of recipients, with recent data suggesting that men are at greater risk of graft rejection and recurrent disease.[111,112]

Hereditary haemochromatosis

Hereditary haemochromatosis (HH) is a disorder of iron homeostasis that predominantly affects Caucasian individuals or those of Northern European descent, with a prevalence of about 1 in 200-300.[113,114] The clinical manifestations of HH vary widely by the number (homozygous or heterozygous) and type of mutant alleles. The two most common pathogenic mutations are C282Y and H63D, though other mutations have less well-defined clinical significance.[113,115] In terms of genotype, HH affects men and women equally. However, mouse models have shown that some HH phenotypes have reduced penetrance in females.[116] As such, men with HH have higher serum ferritin and experience clinically significant iron overload more often than women.[113,117] These differences are attributed to the protective effects of menses in reproductive age women, with regular blood loss via menses reducing risk of iron overload.[114] In accordance with this, men with HH have higher rates of liver injury, fibrosis, cirrhosis, and HCC.[115,118,119] In a large study comparing pathogenic to non-pathogenic HFE alleles, pathogenic alleles were associated with increased all-cause mortality in men but not women.[119] This study also found that men with C282Y heterozygosity were at higher risk of liver injury due to alcohol than women. Finally, men with HH are transplanted more often than women.[120] To our knowledge, there are no studies evaluating sex differences in post-transplant outcomes for HH.

Benign liver lesions

Haemangiomas and focal nodular hyperplasia

Liver haemangiomas and focal nodular hyperplasia (FNH) are the first and second most common benign liver lesions, respectively. Both have a strong female predominance with women accounting for 75-90% of cases.[121,122] Limited reports have commented on the increased size of these lesions with oestrogen exposure.[123,124] One study on haemangioma demonstrated increasing size in pre-menopausal women and men, but a decrease in size in post-menopausal women.[125] However, in general, these lesions are not considered to be oestrogen respo-

nsive and combined hormonal contraception is considered safe in this population.[123] For FNH, there are no data to suggest sex-specific differences in FNH progression or outcomes,[122] with surgical intervention reserved for the rare cases of symptomatic abdominal pain. For haemangioma management, liver transplant may be necessary for large and symptomatic lesions that are not amenable to hepatic resection, which is more common in women, reflecting the higher overall prevalence of the disease in women.[126,127]

Hepatocellular adenomas

Hepatocellular adenomas (HCAs) are 10-fold more common in women than men.[123] Development and growth is promoted by oestrogen, as demonstrated by their association with combined hormonal contraceptive use and growth during pregnancy.[128] Initial management, regardless of size, is cessation of exogenous oestrogens. Although HCAs express progesterone receptors, progestin-only contraception does not appear to promote HCA growth and can be used as an alternative to oestrogen-containing contraception in women with HCAs.[123,129] Given the marked increase in circulating oestrogen levels during pregnancy, HCA growth is common. For lesions of ≥5 cm, intervention by way of embolization or resection can be considered, and monitoring of HCA in pregnancy should include a liver ultrasound per trimester and in the initial post-partum period.[123]

While HCAs are more common in women, the incidence is rising in both men and women. These epidemiologic trends mirror the increasing rates of obesity and metabolic syndrome, with adipose tissue representing a key site of oestrogen production.[130] Weight loss is now a key approach to HCAs, with a recent retrospective study showing that at least 5% weight loss was associated with regression of HCA in female patients with recently discontinued combine hormonal contraception.[130] A small case series also demonstrated HCA regression following bariatric surgery.[131] Ultimately, weight loss should be prioritized in both men and women with HCAs.

In contrast to women, men have a 10-fold higher risk of malignant transformation,[132] which is in part due to their higher risk of being affected by the β-catenin-activated subtype. A careful history should be taken in men for distinct hormonal risk factors that promote HCA development and growth, namely anabolic steroid use.[133,134] Management in men, regardless of β-catenin positivity or size, includes resection or embolization due to their high risk of developing HCC.[135,136] Liver transplant is reserved for men and women whose disease cannot be managed by embolization or resection. Consistent with the higher HCA prevalence in women, nearly 80% of waitlisted or transplanted patients with HCAs are female, although male sex is associated with worse post-transplant outcomes.[137]

Polycystic liver disease

Polycystic liver disease (PCLD) is a genetically inherited liver disease that is characterized by progressive cyst development and growth, affecting about one in one million adults.[138] The autosomal dominant inheritance pattern of PCLD should confer similar risk to men and women,[139] though data from clinical studies are conflicting. One study of 134 patients found similar incidence in men and women,[140] while other data suggest a female predominance with a female to male ratio of 6 to 1 [139]. This discrepancy may relate to more sporadic lesions and clinically apparent disease in women. Female patients do have more symptomatic disease, likely due to the effects of oestrogen on cyst growth.[141,142] The effects of oestrogen on PCLD contrast with its general lack of influence on the growth of simple hepatic cysts outside the context of PCLD. Thus, exogenous oestrogen use should be avoided in women with PCLD. Women with PCLD are also transplanted more often and have better post-transplant outcomes than men. In a recent study of adults transplanted for PCLD over a 20-year period, post-transplant mortality was 46% lower in women than men.[143]

Liver transplantation

Sex disparities in access and outcomes in liver transplantation are well established (Fig. 5). Men account for 60% of liver transplant waitlist registries and almost two-thirds of liver

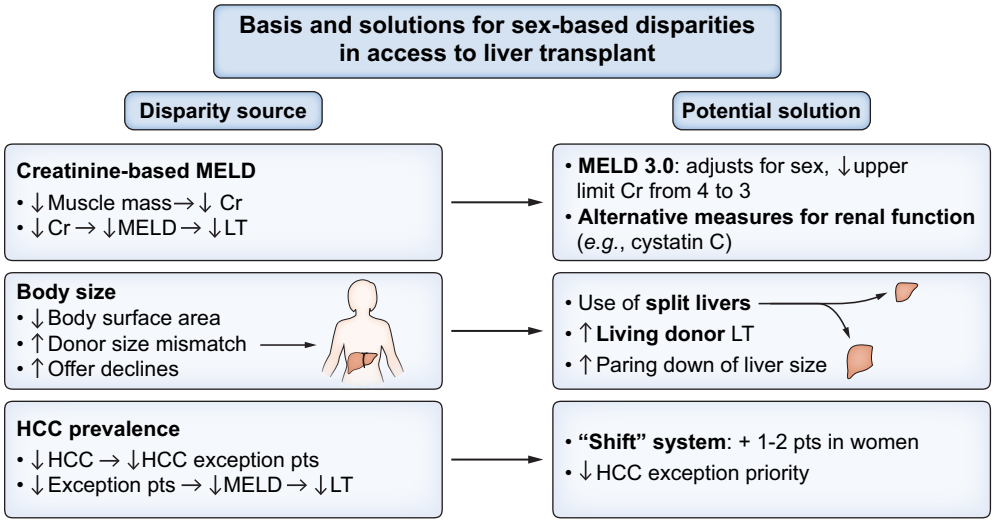

Fig. 5. Basis and solutions for sex-based disparities in access to liver transplantation. Cr, creatinine; HCC, hepatocellular carcinoma; LT, liver transplant(ation); MELD, model for end-stage liver disease; pts, points.

transplants.[144] Women experience more waitlist mortality, and are 20% less likely to undergo liver transplant.[144] This disparity is multifactorial. First, the model for end-stage liver disease (MELD)-based allocation system does not accurately capture degree of renal dysfunction in women, as this system utilizes creatinine levels which are naturally lower in women due to lower muscle mass than men.[145] Smaller height/body size in women also results in increased organ declines due to size mismatch, as deceased donors are more commonly men, with inherently larger organ size.[144,146] Differential priority for HCC MELD exception points is also relevant as the prevalence of HCC is higher in men, who are thus more likely to access organs through this priority pathway.[146,147]

There are several proposed solutions to improving sex disparities in liver transplant access and waitlist mortality. Regarding body mass, options include increased use of split livers and paediatric livers (the latter after being declined by paediatric patients), and surgical paring down of larger livers to accommodate smaller recipients rather than declining these organs and waiting for smaller, size-appropriate organs to become available.[145] Early discussion of living donor transplant is also critical to broadening pathways to transplant, including referral of patients with potential donors to centres that perform these surgeries if living donor transplantation is not available at the patient's existing transplant centre. To address sex disparities in creatinine levels, use of glomerular filtration rate has been shown to help improve waitlist mortality while gender neutral biomarkers such as cystatin C may better capture true renal function in both men and women.[145,148] Further, a variety of measures to improve the allocation system have been studied including using a shift system where women have 1-2 points added to their MELD score.[149] Most notably, MELD 3.0 is an updated version of the current MELD system that has been proposed to address sex-based disparities in organ allocation by including female sex as a component, while capping serum creatinine at 3.0 mg/dl. Studies evaluating MELD 3.0 have predicted it would address much of the sex disparity in liver transplant access and reduce disparities in waitlist mortality for women.[150]

Conclusion

In summary, the epidemiology of many chronic liver diseases differs in men and women, which reflects sex-based differences in innate immunity, metabolism, and endogenous hormones, as well as epigenetic factors including exogenous hormone exposures. While most clinical trial data report composite outcomes in men and women, there is a need for sex-based stratification of treatment response and side effects to help tailor our therapeutic approach in men and women. A growing and robust basic science literature has shed light on potential mechanistic pathways underling sex disparities in liver disease. Evolving translational data using sex-stratified human tissue and clinical models are needed to understand whether such data can inform treatment approaches in humans with liver disease. Finally, there remains a gap in liver-related research among transgender populations, in whom the influence of gender-affirming hormone therapies on chronic liver disease needs to be determined, with the need to consider dedicated representation of this population in emerging clinical trials and epidemiologic studies.

Abbreviations

ADH, alcohol dehydrogenase; AIH, autoimmune hepatitis; ALD, alcohol-associated liver disease; FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; HH, hereditary haemochromatosis; HLA, human leukocyte antigen; IL-, interleukin-; MELD, model for end-stage liver disease; MHT, menopausal hormone therapy; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NK, natural killer; PBC, primary biliary cholangitis; PCLD, polycystic liver disease; PCOS, polycystic ovary syndrome; PSC, primary sclerosing cholangitis; STAT-3, signal transducer and activator of transcription 3.

Financial support

MS receives grant support from the NIDDK (DK111944/DK131238). DD receives grant support from the NIAAA (AA017986).

Conflict of interest

MS receives grant support from Zydus pharmaceuticals and GSK.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

KC: Drafting of manuscript, initial figure design and editing. MD: Drafting of manuscript. DD: Drafting of manuscript. MS: Drafting of manuscript, final manuscript review, editing and approval.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100870.

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