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Gender and liver

Margherita Marocchi[1], Veronica Bernabucci[1], Erica Villa[1]

1. Department of Internal Medicine, Gastroenterology Unit, Università degli Studi di Modena & Reggio Emilia, and Azienda Ospedaliero-Universitaria di Modena, Modena, Italy — *Received 29 October 2015; accepted 18 December 2015.*

Summary. Chronic liver diseases (CLD) show significant differences in incidence and evolution according to sex. Traditionally, the natural history of viral-associated CLD is considered to be more favorable in females, with slower progression to fibrosis and better therapeutic response. This scenario totally changes when women get older and enter menopause. The liver, though not a classical target for sex hormones, is very sensitive to the action of estrogens, which are supposed to have a protective role in preventing progression of liver injury towards fibrosis. In chronic hepatitis B, HBV-DNA is higher in males than in females, with increased risk of hepatocellular carcinoma (HCC), which becomes comparable after menopause. The natural history of chronic hepatitis C is the most studied with strong evidence showing that the progression of fibrosis in men is more severe but presents a clear trend over the years. In women instead, fibrosis progression is very slow during reproductive age, but accelerates rapidly after menopause. In parallel, we are witnessing an increase of steatosis and therefore of the inflammatory status which contributes to accelerate the fibrogenic process. In addition, women in childbearing age have a higher rate of response to antiviral treatment when compared to men, which decays soon after the onset of menopause. Clearly, once having established the protective role of estrogens, various studies have been conducted to evaluate the efficacy of the association between PEG-IFN and ribavirin with hormone replacement therapy or drug modulators of estrogen receptors, but without promising results. The first generation of protease inhibitors (boceprevir) showed greater efficacy in inducing a sustained virologic response in genotype 1 menopausal women with previous treatment failure. Preliminary data with the new IFN-free treatment regimens suggest that the power of these drugs is such as to overcome the resistance of the menopausal women to traditional therapy.

Key words. Gender, chronic liver disease, estrogens, menopause.

Genere e fegato

Riassunto. Le malattie epatiche croniche presentano notevoli differenze di genere in termini di evoluzione e di complicanze: tradizionalmente la storia naturale delle epatopatie virali croniche è più favorevole nel sesso femminile che in quello maschile, con progressione più lenta verso la cirrosi, minor incidenza di complicanze, tra cui il carcinoma epatocellulare (HCC), e migliore risposta terapeutica. Tuttavia questo scenario si modifica radicalmente quando compare la menopausa, in quanto il fegato, pur non essendo classicamente un organo bersaglio per gli ormoni sessuali, è comunque sensibile all'effetto degli estrogeni, che sembrano svolgere un ruolo cruciale nella progressione della fibrogenesi. Nell'infezione virale B, i livelli sierici di HBV-DNA sono più elevati nell'uomo rispetto alla donna e si associano quindi a un aumentato rischio di sviluppo di carcinoma epatocellulare (HCC). Con la menopausa il rischio di sviluppo di HCC tende a diventare equivalente nei due sessi. La storia naturale dell'epatite cronica C è quella maggiormente studiata negli anni, con forti evidenze che dimostrano come la progressione della fibrosi negli uomini sia più severa e presenti un andamento lineare. Nelle donne invece è molto lenta in età fertile, ma accelera rapidamente dopo la menopausa. Parallelamente si assiste a un incremento della steatosi e dello status infiammatorio, due fattori che contribuiscono al processo di fibrogenesi. Inoltre, le donne in età fertile presentano un'elevata percentuale di risposta al trattamento antivirale se comparate agli uomini, che decade poco dopo l'insorgenza della menopausa. Chiaramente, una volta assodato il ruolo protettivo degli estrogeni sono stati condotti vari studi volti a valutare l'efficacia dell'associazione tra interferone peghilato (PEG-IFN) e ribavirina con terapie ormonali sostitutive o con farmaci modulatori degli estrogeni, ma con risultati non promettenti. Gli inibitori delle proteasi di prima generazione (boceprevir) hanno dimostrato un'efficacia maggiore nell'indurre una risposta virologica sostenuta in pazienti menopausali di genotipo 1 con precedente fallimento terapeutico. Dati preliminari con i nuovi regimi di trattamento IFN-free suggeriscono che la potenza di tali farmaci sia tale da superare anche la resistenza delle donne menopausali alle terapie tradizionali.

Parole chiave. Genere, malattie epatiche croniche, estrogeni, menopausa.

Introduction

"Men come from Mars and women come from Venus," said someone once to underline the huge amount of differences existing between men and women at all ages. This is surprisingly true also when it comes to health; for example, cardiovascular diseases mainly affect males, at least at a young age, bone disease belongs almost exclusively to women and also chronic liver diseases (CLD) show relevant differences in incidence and evolution according to sex. Traditionally, CLD have a more severe course in men, with rapid evolution to cirrhosis and increased

risk of developing hepatocellular carcinoma (HCC). At the same time, chronic liver diseases with diverse etiology occur differently in males or in females. Autoimmune disease, including primary biliary cirrhosis, is almost exclusive to women, with the exception of LKM-positive autoimmune hepatitis, which shows similar incidence in both sexes. Primary sclerosing cholangitis is instead a male-only prerogative, and anecdotal cases are found in women. The situation is no different when it comes to viral hepatitis: the natural history of HCV-associated CLD is considered to be more favorable in females, with slower progression to significant fibrosis and better therapeutic responses.

Fibrosis and gender

This scenario totally changes, as seen in many other diseases, when women get older and enter menopause. Hence, the common denominator explaining all these differences seems to be the effect of estrogens, which are supposed to have a protective role in preventing progression of liver injury towards fibrosis. The liver, though not a classical target for sex hormones, is very sensitive to the action of estrogens. Target tissues with reproductive functions display the highest amount of estrogen receptors (ERs), but also non-classical target tissues, like the liver, have variable quantities of ERs. The physiological effectors for estrogen sensitivity of any tissue, represented by α and β estrogen receptors, are both present in the liver[1-3]. Over the years relevant data from in-vitro and in-vivo studies suggested a crucial role for estrogens as protective factors in hepatic fibrogenic processes. Experimentally, estrogens were shown to have a relevant fibro-suppressive role in the rat model of di-methyl-nitrosamine (DMN)-induced liver damage and particularly the fibrotic response of the female liver to DMN treatment after ovariectomy was significantly weaker than that of the male liver, suggesting that physiological levels of estrogen have an antifibrogenic effect[4-5]. In the past years, a paper by Di Martino et al.[6] showed an accelerated progression of fibrosis in women with chronic hepatitis C (CHC) after menopause which benefited from prolonged periods of hormone-replacement therapy (HRT). Most likely, long hormonal exposure during fertile years, pregnancies and HRT would exert a beneficial effect on the inflammatory status of a woman in general and particularly on the liver. In HCV infection this would result in a slower progression toward severe fibrosis and subsequent cirrhosis. This was later confirmed by Codes et al.[7] who underlined the importance of cofactors, such as metabolic features, almost irrelevant during fertile years, which become instead extremely conspicuous after menopause. Estrogen deprivation induces a rapid onset or a rapid worsening of the metabolic syndrome (increased intra-abdominal fat, atherogenic lipid profile, steatosis, insulin resistance) suggesting that the higher severity of liver disease after menopause may be at least partly explained by the occurrence of metabolically-mediated damage in association with that induced by the virus. Significant differences in the rate of fibrosis progression between men and women were first proposed by Poynard et al.[8] Interestingly, higher progression of fibrosis was also evident in older women, but this was attributed to age and not to hormonal deprivation. Furthermore, physiological fluctuations of sexual hormones in women with CHC are accompanied by consensual modifications of pro-inflammatory and anti-inflammatory cytokines levels, indirectly affecting the rate of progression of hepatic fibrosis[9]. In men instead, estrogen levels and estrogen-dependent pro-inflammatory cytokines constantly maintain levels comparable to those of postmenopausal women, i.e., low and high respectively. Fibrosis progression rate is certainly related with etiology of CLD: HIV–HCV co-infected patients show the most rapid progression (50% cirrhosis percentile at 52 years of age) while the slowest is primary biliary cirrhosis (PBC - 50% cirrhosis percentile at 81 years). In alcoholic liver disease, the fibrosis progression is more rapid in females, confirming the extreme sensitivity of women to alcohol-induced liver damage. With regard to hepatitis B, it is interesting to note that anti-HBe positive patients have earlier transition to septal fibrosis in comparison with HBeAg-positive patients and in the case of concomitant delta chronic hepatitis fibrosis progression is definitely faster than in patients with chronic hepatitis B alone. HBV-DNA viral load directly correlates with the risk of HCC[10]. Our group recently published a study confirming that reproductive status is associated with fibrosis severity in women with CHC. A cohort of 87 CHC women naïve to previous antiviral treatment were stratified in four groups according to reproductive stage, respectively: full reproductive age, premenopausal including women who entered menopause (defined as no menstrual period for 12 consecutive months within 5 years from enrollment in the study), early menopausal (i.e., menopause present at the time of enrollment for less than 5 years) and late menopausal (menopause present at the time of enrollment for at least 10 years) and pair-matched by age with four groups of male patients. Data showed a discontinuous progression of fibrosis in women, with a very slow trend during reproductive age and a sharp increase soon after the onset of menopau-

se. The contemporary evaluation of inflammatory activity showed a parallel behavior of inflammation and fibrosis: very mild during reproductive age with a sudden increase with menopause[11]. As shown in Figure 1, there was a significant difference between males and females in the first two age groups (fertile age and pre-menopausal age) while in early menopausal age and in the very late menopausal group the difference was not significant[12].

Epidemiological studies report a higher prevalence of NAFLD in males compared with females, which becomes even higher in menopausal females than in reproductive-age women (Table 1).

In the entire cohort (males and females), childbearing age was associated with a trend towards a lower prevalence of significant (stage F2-F4) liver fibrosis, in comparison with menopausal females but not with the cohort of males. Men in groups paired with the first three female groups (reproductive age, pre-menopause, early menopause) showed remarkably more severe liver disease, as indicated by mean stage of fibrosis (Figure 1), but no significant difference in fibrosis was found between women in the late menopausal group and age-matched men. Similarly, no significant difference in the presence of cirrhosis was observed between male–female pairs correlating with full reproductive age and late menopause, whereas the incidence of cirrhosis was significantly lower in the two intermediate groups of women than in age-matched groups of men. We then assessed the impact of menopausal status on the severity of liver damage in females with non-alcoholic fatty liver disease (NAFLD). Clinical evidence is further supported by data obtained in a model of overfed male and female zebrafish. Old overfed female zebrafish developed hepatic steatosis and fibrosis in a manner similar

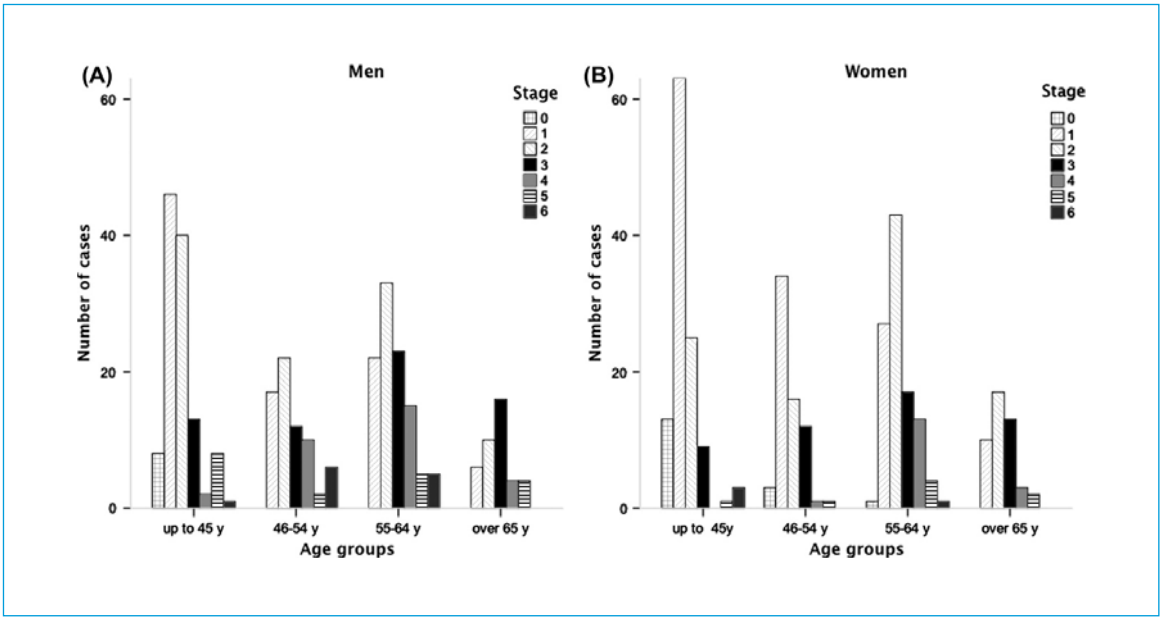

Figure 1. Number of cases belonging to different histologic stages grouped by gender (panel A: Men; panel B: Women) and reproductive phases (fertile, pre-menopause, early menopause, late menopause). Modified from Bernabucci et al, 2014[13].

Table 1. Distribution of hepatic steatosis in females across different age groups. The distribution across groups is statistically significant (p <0.027). Modified from Bernabucci et al, 2014[13].

	Age groups			
Steatosis	< 40 y	42–50 y	52–64 y	> 65y
Absent	56	58	81	25
Up to 20%	16	29	42	8
More than 30%	1	9	9	8
Total	73	96	132	47

to overfed males (both young and old). In contrast, young female fish, despite a high increase in body mass index (BMI), developed less steatosis and were completely protected from the development of fibrosis. Overfeeding seems to be able to trigger a series of events that lead first to liver steatosis and then to fibrosis, and that ovarian senescence increases the risk of fibrosis. These data in zebrafish, together with the inhibitory effect of estradiol on expression of TGFβ1, TNF-α, IL-6 and IL-1b, also suggest a protective effect of fertile status on the severity of liver damage in NAFLD. The marked up-regulation of hepatic TNF-α and IL-6 at the time of early menopause, becoming non-significant in late menopause, could explain the strong but selective association we observed between liver fibrosis and early menopause[14-15].

Gender and HCC risk

Male sex is known to be an important risk factor for HCC. This could be linked with some risk factors known to be more frequent in males, like HBV infection and/or alcohol consumption. However, after menopause HCC incidence is comparable between men and women[16]. By now, the possible role in HCC development of the different hormonal features between the two sexes during the lifetime has been deeply explored by in-vitro and in-vivo studies. Experimental data demonstrated a delay in the development of DEN-induced HCC, after androgen receptor expression knockout in hepatocytes, suggesting the active androgen receptor pathway in increasing the risk of the HCC appearance[17]. On the other hand, studies from the same DEN-induced HCC animal model indicated a possible favorable effect of estrogen in female HCC in terms of protection of hepatocytes from malignant transformation via down-regulation of IL-6 release from Kupffer cells. On the clinical side, a multicenter case-control study conducted in 2003 in Taiwan[18] evaluated the effects of reproductive factors on HCC risk. They reported an association between reproductive events and exogenous estrogen use and HCC among women with HCC related to HBV or HCV infection. In this study, HCC risk was inversely related to the age at natural menopause. Oophorectomy performed at age 50 or younger during premenopausal years was also a risk factor for HCC.

Response to antiviral therapy

In the past years, differences between men and women response rate to antiviral therapy were merely ascribed to age. Hayashi et al.[19] showed that women younger than 40 years of age under standard treatment with alpha-interferon for chronic hepatitis C had higher rates of sustained virologic response (SVR) than men (75% vs. 33%); however, this advantage was lost after 40 years of age. Sezaki et al.[20] retrospectively evaluated the influence of gender on treatment of genotype 1 chronic hepatitis C, concluding that SVR to pegylated interferon alpha plus ribavirin (PEG-IFNα/RBV) was poorer among HCV positive females older than 50 years than in HCV positive males (32% vs. 63%). Therefore, older age is known to be a negative predictive factor for SVR, but menopause coincides with older age and the influence of menopause itself on response to antiviral therapy had never been properly investigated[21-22]. Our group in 2011 demonstrated that age is not independently correlated with SVR, whereas menopause is, indicating that menopause is associated with a remarkable and unrecognized resistance to antiviral therapy, especially in carriers of genotype 1 HCV[11]. A plausible explanation for this finding lies in the up-regulation of hepatic TNF-α and circulating IL-6 occurring at the time of menopause. Both these cytokines undergo relevant changes during menopause[9] and in HCV infection, during which their levels are greatly up-regulated, and they are able to interfere with antiviral response[23-24]; the occurrence of menopause is associated with a large additional increase in circulating IL-6 levels, a further increase in hepatic TNF-α levels, and an expression enhancement of suppressor of cytokine signaling 3 (SOCS3) in the liver. TNF-α has been implicated as an independent factor associated with response to IFN and hepatic SOCS3 is reported to be the strongest factor influencing the outcome of interferon-based antiviral therapy. SOCS3 expression is indeed significantly associated with response to antiviral therapy and this association is genotype-dependent; HCV core directly up-regulates SOCS3 expression and a peculiar genetic background of SOCS3 (i.e., specific polymorphisms) per se might explain the nonresponse of many HCV positive patients to antiviral therapy in a genotype-specific manner. Recent evidence showed that genotype 1b C virus links HCV core with SOCS3 activating receptors; likely, specific genetic sequences of the genotype 1b viral genome might exert a direct induction of SOCS3 expression[25-29]. These data support the hypothesis that menopause determines a switch to a systemic and hepatic proinflammatory status in which increased IL-6 and TNF-α production contributes to IFN resistance[9]. Women entering menopause rapidly go from an estrogen-protected environment, where HCV-mediated inflammation is limited, to an estrogen-deprived one in which inflammation becomes less controlled and resistance to antiviral therapy increases remarkably, thus increasing the risk of de-

veloping severe fibrosis. Clearly, given the established protective role of estrogens in liver fibrosis progression and their implications in loss of response to antiviral treatments, there has been growing interest over the years in evaluating the effects of hormone-replacement therapy (HRT) or of estrogen receptor modulating drugs in addition to standard antiviral therapy for HCV. A Japanese group published a study in 2012 on 123 post-menopausal women with CHC treated with dual antiviral therapy with the addition of raloxifene (RLX) or with standard of care (SOC). At a distance of 24 weeks after treatment, the SVR rate was significantly higher for RLX plus SOC patients (61.3 %) than for SOC-only patients (34.4 % - $p < 0.0051$)[30]. As RLX has been shown to inhibit serum IL-6 and TNFα synthesis, the authors suggested that the derived inflammatory inhibition would lead to decreased cytokine production thus determining higher sustained virologic response (SVR) rate in anti-HCV treatment. In 2008 we carried out a prospective randomized trial of standard antiviral therapy combined with HRT started 3 months before PEG-IFNα/RBV in the concept that reversal of estradiol levels to pre-menopausal could improve SVR. In contrast with the Japanese study, our results do not seem to support a role for HRT in improving SVR (personal communication). The very low SVR rate and the high rate of relapse and failure with dual therapy led us to carry out a pilot study on triple therapy with first generation protease inhibitors (boceprevir - BOC) in addition to standard therapy in difficult-to-treat genotype 1 CHC menopausal women[31]. Boceprevir plus SOC determined a striking effect: viral load became undetectable in almost 60% of patients after 4 weeks and in more than 70% at week 12, and SVR was obtained in 45% of women. Therefore, rapid virologic response (RVR) proved to be the only independent predictor of SVR and none of the other factors traditionally associated with achievement of SVR (i.e., low viral load at baseline, absence of fibrosis or cirrhosis, IL 28B genotype, >1 Log decrease in HCV RNA) were independently related to SVR[31]. In conclusion, boceprevir plus standard PEG-IFN-α/RBV therapy was effective in achieving SVR in about 50% of menopausal women with genotype 1 chronic hepatitis C who had failed SVR with prior PEG-IFN-α/RBV treatment. Most importantly, BOC-based triple therapy success rate was not influenced by the pattern of previous response to standard therapy or by the severity of liver fibrosis while RVR BOC was the only independent predictor of SVR (Table 2). Indeed, in our data neither estimated duration of HCV infection nor the age of acquisition of HCV infection was independently associated with severe fibrosis while levels of circulating estradiol were. Furthermore, onset of

Table 2. Univariate and multivariate analysis for factors predicting sustained virologic response. BMI, body mass index; HCV, hepatitis C virus; ALT, alanine aminotransferase. Modified from Bernabucci et al, 2014[31].

Variables	Univariate analysis OR (95% CI)	*P* value	Multivariate analysis OR (95% CI)	*P* value
Age (yr)	1.006 (0.916-1.105)	0.900		
Age at menopause	1.150 (0.931-1.450)	0.195		
Previous response	2.662 (0.957-6.881)	0.043	2.927 (0.931-9.206)	0.066
Histological grading	0.894 (0.605-1.322)	0.576		
Histological staging	0.982 (0.586-1.645)	0.946		
Fibrosis	1.667 (0.528-5.265)	0.384		
Liver stiffness	0.986 (0.895-1.086)	0.774		
Cirrhosis	1.111 (0.155-7.974)	0.917		
BMI	1.000 (0.825-1.212)	1.000		
HCV RNA > 800.000 IU/mL	0.519 (0.120-2.248)	0.381		
RVR	1.200 (0.070-20.429)	0.900		
1 log decline at week 4	3.733 (1.676-12.658)	0.034	0.961 (0.194-4.757)	0.961
RVR BOC	7.347 (2.156-25.035)	0.001	6.794 (1.596-21.644)	0.010
ALT (IU/mL)	0.996 (0.977-1.014)	0.645		
Platelets ($\times 10^3$/mm^3)	1.000 (1.000-1.000)	0.165		
HOMA	0.907 (0.533-1.544)	0.719		

menopause was significantly correlated with necro-inflammation, steatosis and metabolic alterations (high cholesterol and glucose levels)[32].

On the whole, human and experimental data underline the importance of looking at the relationship between gender and liver disease in a comprehensive manner, evaluating the etiology of viral disease, as well as the influence of reproductive status and metabolic factors. Preliminary data with the new IFN-free treatment regimens suggest that these drugs have the power to overcome the resistance of menopausal women to traditional therapy.

Key messages

- The natural history of viral-associated chronic liver disease is more favorable in women, with slower progression to relevant fibrosis and better therapeutic response.
- Estrogens have a protective anti-fibrogenic role in the liver, which is lost with menopause, and causes, in women, a rapid progression of liver fibrosis and negatively influences response to antiviral treatments.
- Fibrosis progression is very slow during reproductive age, but accelerates rapidly after menopause; in parallel, antiviral response rate decreases.
- Menopausal HCV positive women are a high-risk population for developing cirrhosis with lower response rate to standard antiviral treatment.
- New IFN-free treatment regimens could overcome the resistance of the menopausal women to traditional therapy.

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Correspondence to:
Erica Villa
Department of Internal Medicine, Gastroenterology Unit,
Università degli Studi di Modena & Reggio Emilia,
and Azienda Ospedaliero-Universitaria di Modena, Modena, Italy
Tel. +390594225308
Fax +390594222624
email erica.villa@unimore.it