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Gender differences in liver disease and the drug-dose gender gap

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Abstract

Although gender-based medicine is a relatively recent concept, it is now emerging as an important field of research, supported by the finding that many diseases manifest differently in men and women and therefore, might require a different treatment.

Sex-related differences regarding the epidemiology, progression and treatment strategies of certain liver diseases have long been known, but most of the epidemiological and clinical trials still report results only about one sex, with consequent different rate of response and adverse reactions to treatment between men and women in clinical practice.

This review reports the data found in the literature concerning the gender-related differences for the most representative hepatic diseases.

Key words: gender, liver toxicity, liver disease, systematic review

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Introduction

Gender-based research has expanded significantly in the last years, based on the premise that males and females show differences in the prevalence, pathophysiology and manifestations of several diseases. Such differences also manifest in the pharmacological treatment, which can differ in terms of required dose, administration timing and higher risk of adverse drug reaction in females compared to males [1].

Despite most of the clinical trials have included mainly patients of one sex, there is much evidence that certain liver diseases develop, manifest and are treated differently according to gender [2].

So far, the liver has also been described as a sexually dimorphic organ responsive to sex hormones by expressing androgen and estrogen receptors: this would explain to some extent the disparity found in gene expression pattern, immune response and xenobiotic metabolism between men and women [3, 4].

In this review we present the main gender-based differences reported in the literature with regard to the prevalence, prognosis and treatment of diverse liver diseases.

1.   Drug toxicity and the 'drug-dose gender gap'

Many studies have proven that women respond differently, and more often develop adverse reaction, to several drugs compared to men. The relative weight difference that exists between male and female sex, leading to a higher concentration and drug exposure in females, was considered to be a detrimental factor in order to explain this so called 'drug-dose gender-gap' [1], but it has so far been discounted.

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Excluding behavioural or dosing differences, three mechanisms would explain the gender-based differences seen in drug response and susceptibility to toxic effects: gender differences in pharmacokinetics, gender-specific hormonal effects or interaction with signalling molecules that can affect drug effect and safety and differences in aberrant immune response targeting the organs following drug exposure [5].

Gender-based differences that can influence drugs pharmacokinetics include variations in gastric acid secretion, gastrointestinal and renal blood flow, a different drug/plasma protein binding profile, the relative percentages of muscular and adipose tissue and physiologic and hormonal changes during the menstrual cycle [5, 6] (Figure 1).

Gender-specific differences in gene expression or activity of drug metabolizing enzymes and transporters have been proved [7]. Males have higher glucuronidation rates, mainly via UDP-glucuronosyltransferases (UGT) activity, therefore greater paracetamol clearance than women [8]. Also, differences in major drug metabolising enzymes belonging to the cytochrome P450 family are clearly established: for instance, CYP3A4 is more expressed in women [9].

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Figure 1. Major determinants of gender-based differences in liver toxicity and damage
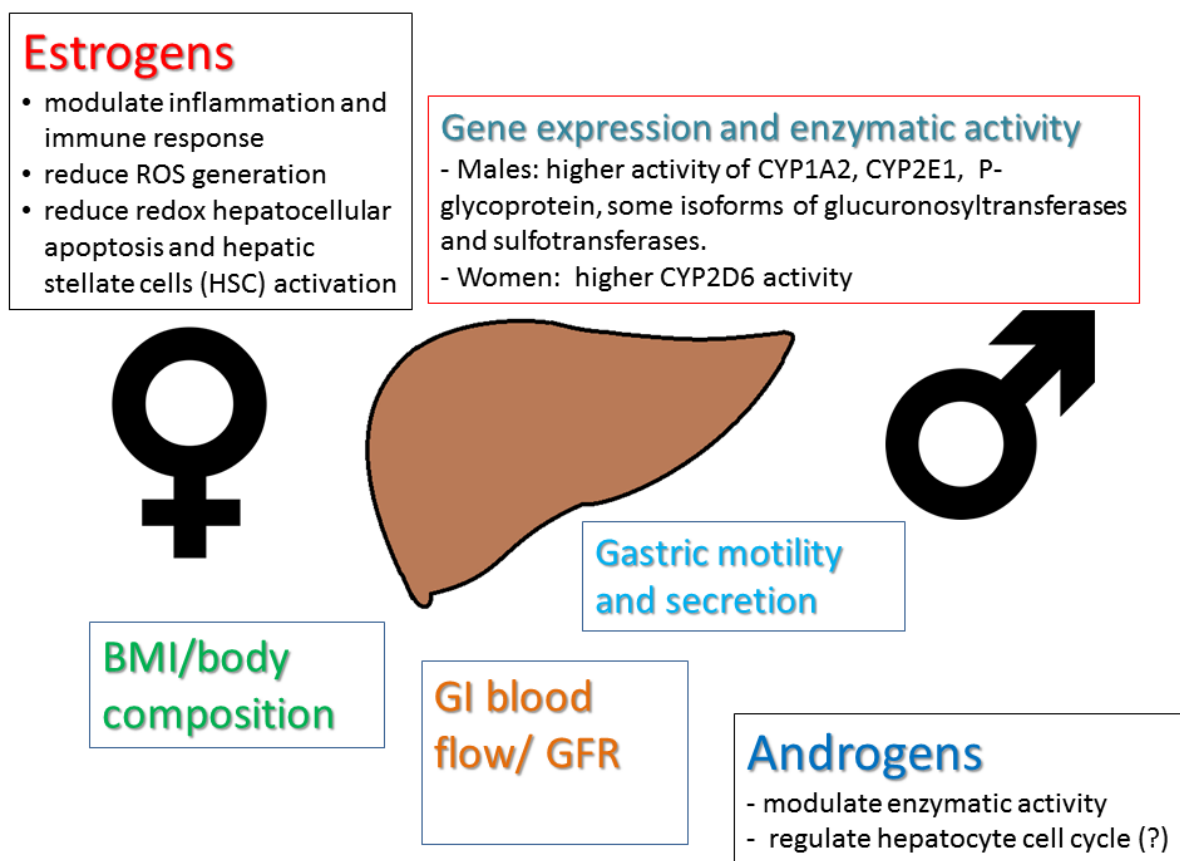
Abbreviations: ROS, reactive oxygen species; BMI, body mass index; GI, gastrointestinal; GFR, glomerular filtration rate; CYP, cytochrome P450 isoenzyme.

2. Liver disease from toxic cause

2.2 Drug-induced liver injury (DILI)

Drug-induced hepatotoxicity is often the reason for the withdrawal of drugs from the market and the major cause of acute liver failure in western countries with a high percentage of cases requiring liver transplant [10]. Its annual incidence in the general population ranges between 14 and 19 events per 100.000 inhabitants, with almost one third developing jaundice [11, 12].

All drug-induced adverse reactions can be classified into intrinsic or idiosyncratic adverse reactions [13]. Intrinsic adverse reactions are those usually caused by drugs that predictably

induce liver injury in a dose-dependent manner. Idiosyncratic adverse reactions are less related to dose, more rare and varied at presentation and tend to develop in susceptible individuals.

With a few exceptions, the main being paracetamol-induced direct hepatotoxicity, most of drug-induced-liver-injury (DILI) cases in humans are considered to be idiosyncratic. Although idiosyncratic DILI is not directly related to drug dose, several data show that most of idiosyncratic cases do occur at high drug concentrations [14], implying therefore a less strict sense of the conventional dose-independency definition.

The majority of DILI episodes are self-limited and resolve after cessation of the causative agent, although about 18% of patients will progress to chronic DILI [15], defined as continued injury six months after the initial diagnosis [16].

Idiosyncratic DILI usually involves damage to hepatocytes with various degrees of necrosis and apoptosis with consequent hepatitis symptoms and biochemical alterations, while allergic drug-induced liver reactions are characterised by an IgE immune response and can be associated with systemic manifestations such as rash, fever and eosinophilia [10].

In cholestatic type reactions, injury to bile duct cells and components is prevalent, leading to jaundice and pruritus and, in more severe cases, to vanishing bile duct syndrome [17]. Other possible types of DILI include granulomatous, steatohepatitis, autoimmune, fibrosis reaction and oncogenetic activation.

From a histological perspective, acute and chronic hepatitic, acute and chronic cholestatic and mixed hepatitis-cholestatic patterns are the most common of the eighteen patterns identified by the Drug-Induced Liver Injury Network (DILIN) [18].

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Drug properties possibly linked to DILI risk in humans are dose threshold, lipophilicity, formation of reactive metabolites, mitochondrial liability, inhibition of ATP-dependent bile salt export pump (BSEP) and other hepatobiliary transporters.

It has been reported that females have about 1.5 fold greater risk of developing an adverse drug reaction compared to males [19]. This is mainly due to gender-based differences in pharmacokinetics and pharmacodynamics but also to differences in immune response and inflammation corresponding to a higher level of hepatic pro-inflammatory cytokines, higher antibody production and more severe hepatitis in females compared to males [20]. Also, sex hormones may play a role, with estrogens reducing liver injury while progesterone contributing to liver damage, likely modulating inflammation and immune response, as seen in animal models [21].

In addition, a different susceptibility and response to toxicity in hepatocytes and cholangiocytes depending on sexual dimorphism (XX vs. XY), as showed in neurons and splenocytes, has been postulated [22, 23].

A female predominance of drug-induced hepatitis has been observed for several drugs while chronic liver injury, for instance due to azathioprine, has been seen mostly in men, although prevalence and incidence slightly vary among countries [24].

In a French population-based study, the incidence rates of adverse hepatic reactions induced by drugs were similar in males and females until the age of 50 years but then became twice as high in women as in men [11].

The DILIN analysed 899 patients with DILI in a prospective cohort study in the US: 59% of patients were women and the most common agents implicated in short-latency DILI cases

were anti-infective agents (moxifloxacin, azithromycin, ciprofloxacin, rifampin, and levofloxacin). Agents more frequently implicated in long-latency DILI cases were minocycline, statins, amiodarone, mercaptopurine, atomoxetine, tamoxifen, oxaliplatin and interferon β [15].

In another prospective study from Iceland involving 96 patients diagnosed with DILI, 56% were females and the most common involved drugs were amoxicillin/clavulanate, diclofenac, azathioprine, infliximab, nitrofurantoin [12].

Antibiotic agents were also the more frequently associated with hepatotoxicity in a cohort of 461 patients with DILI registered in southern Spain [25]. In this cohort of patients, males represented the majority of idiosyncratic hepatotoxicity cases (52%), while almost all patients who developed drug-induced fulminant hepatic failure were females (89%) [25].

The Acute Liver Failure Study Group has demonstrated a female preponderance in acute liver failure due to either paracetamol (74%) [26] or idiosyncratic drug-induced adverse reactions (67%) [27].

So far, this evidence supports that women are at increased overall risk for DILI and more likely than men to present with or progress to acute/fulminant liver failure.

2.2 Alcoholic liver disease (ALD)

Alcohol abuse is a well-known risk factor for progressive liver disease leading to cirrhosis and end-stage liver disease [28].

The prevalence of alcohol drinking varies among countries and according to gender, with rates from 3 to 94% for women and from 37 to 97 % for males [29].

In a recent systematic review on sex differences in alcohol use, women were found to consume less alcohol than men, to drink less frequently, and to be less likely to become hazardous drinkers [30].

Alcohol-induced liver injury encompasses mechanisms such as generation of reactive oxygen species (ROS) from hepatic alcohol metabolism, oxidative stress, loss of protective liver enzymes and transporters and release of pro-inflammatory cytokines, also sustained by the immune activation in response to increased level of gut-derived endotoxin induced by ethanol exposure [31].

It has been shown that risk of progression to alcohol-induced cirrhosis increases with a daily intake of alcohol higher than 30 g/day [32].

Based on the epidemiological evidence of a threshold effect of alcohol, a limit of 16 g/day in women and 24 g/day in men has been suggested in order to prevent liver damage [33, 34]. However, data suggest that even a lower quantity of alcohol may be toxic in women, therefore a threshold of no more than 60 g per week should be suggested [35].

Several studies have proved that female sex is more susceptible to the toxic effects of alcohol: women develop ALD and progress to alcoholic cirrhosis after a shorter period of heavy drinking compared to men and at a lower level of daily drinking [36]. Results from a systemic meta-analysis on alcohol as a risk factor for liver cirrhosis and related mortality, showed that women had higher relative risk than men for development of cirrhosis and mortality for the same amount of drinking [37].

One of the explanations for the lower alcohol toxic threshold seen in females is the lower level of gastric alcohol dehydrogenase compared to males. This would lead to lesser gastric

oxidation of ethanol and therefore an increment in its bioavailability [38]. A different composition in total body water and fat may influence alcohol distribution [5].

In addition, females have a higher inflammatory activation in response to increased gut-derived endotoxin caused by alcohol exposure compared to males: estrogen seems to have major influence on the susceptibility of Kupffer cells to gut-derived lipopolysaccharide and this would result in increased pro-inflammatory cytokine production [39, 40], worse inflammation and higher risk of liver disease progression.

3. **Autoimmune liver disease**

3.1 Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is a disease of the hepatic parenchyma defined by progressive inflammatory destruction, circulating autoantibodies, hypergammaglobulinaemia and interface hepatitis on histology [41].

AIH is highly prevalent in female sex, with women representing the 70–90% of affected patients, with a double peak distribution in terms of age at diagnosis/first presentation (between 10 and 30 years or during late middle age) [42]. Prednisone alone or in combination with azathioprine is the established treatment of AIH [43].

Histocompatibility leukocyte antigens (HLA) DR3 and HLA DR4 are susceptibility factors for type 1 AIH in Caucasian Northern European and North American patients [44, 45], while HLA DR4 is predominant in Japanese patients [46]. HLA DR4 occurs more commonly in women than men with type 1 AIH and it has been associated with concurrent immune diseases and remission during corticosteroid therapy, while HLA DR3 has been associated with early age onset and treatment failure [47, 48].

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Whether disease expression and outcome differ according to gender and whether HLA DR3 and DR4 have a synergism with gender is poorly understood, and available studies show discrepant findings.

Czaja et al analysed a cohort of 185 well-defined AIH patients and did not find any significant gender-based difference in terms of response to steroid treatment, whereas HLA haplotype (DR3 or DR4) was the only predictor of treatment failure and risk of progression to liver failure/ liver transplant in women, with HLA DR3 being associated with failed treatment response in both genders [49].

In another study involving a highly-selected European cohort of 238 patients with AIH, men appeared to have better long-term survival and outcome than their female counterparts independently of HLA allotype [50].

In a Japanese study evaluating clinical features of AIH male patients, the frequency of normalization of the serum ALT level within six months after the beginning of corticosteroid treatment was significantly lower in men (73%) as compared with women (93%) [51]. Nonetheless, the number of male patients was limited and the statistical difference in response was marginal. In addition, 36 patients were treated with ursodeoxycholic acid or a combination of lower doses of prednisolone and UDCA; the role of UDCA on the outcome of patients with AIH is at least uncertain [52].

It is still not clear whether gender (particularly female sex) confers only a susceptibility to the development of AIH or it has an influence on drug response, and if so, by itself or by modulation of the immune response. Indeed, it has been postulated that sex hormones may play a role in systemic immunologic response by influencing maturation of adaptive

lymphocytes, antigen presentation and cytokine secretion after binding to hormone receptors expressed by immune cells[53].

3.2 Primary Biliary Cholangitis

Primary Biliary Cholangitis (PBC) is an autoimmune liver disease, consisting of a chronic non-suppurative destructive cholangitis which affects women ten times more often than men. Ursodeoxycholic acid (UDCA) is the only recognised medical treatment at the moment, with liver transplantation as a final option for those cases that progress to end-stage liver disease [54].

PBC is highly variable in terms of clinical impact on patients, and one of the main aspects of this is the response to UDCA treatment: a significant subgroup of patients has a suboptimal biochemical response to UDCA thus predicting a poor outcome [55, 56] although it has been suggested that the UCDA "response" might actually represent spontaneous biochemical improvement unrelated to the medication [57].

Whether the disease phenotype is the same in PBC male and female patients is still unclear and not studied in depth, mainly because of the rarity of male patients and the difficulty in developing adequately powered cohorts. So far, satisfactory reasons to explain the rarity of PBC in males are still lacking.

Clinically speaking, women tend to present with pruritus as first symptom more often than males [58].

A recent study from the United Kingdom Primary Biliary Cholangitis (UK-PBC) consortium investigated the impact of gender in predicting prognosis in PBC in a cohort including 2353 non-transplanted PBC patients [59]. Men presented at an older age and with a more severe

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disease and male sex was an independent risk factor for non-response to UDCA on multivariate analysis. Also, female sex revealed a clear age-related difference in response to UDCA: women presenting younger than the age of 45 (the age of equivalent likelihood of response between the groups) were significantly less likely to respond to UDCA than either men or older women at presentation, with age again being an independent predictor of UDCA response on multivariate analysis.

The inclusion of patients from every PBC centre in the United Kingdom and the size of the cohort make these data very useful for clinical practice. Moreover, the age and gender association with non-response could help to tailor novel therapies, e.g. estrogen-targeting therapies might have a role in non-UDCA-responding young female patients.

3.3 Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic condition in which inflammation of the bile ducts, both intrahepatic and extrahepatic, lead to cholestasis and progressive hepatic fibrosis [60].

The most accredited pathophysiological theory is the activation of a persistent immune-mediated damage to cholangiocytes following the exposure to infective or toxic agents, with progressive destructions of bile ducts and chronic cholestasis [61].

PSC cannot be considered as a classical autoimmune disease, as it occurs with male predominance (M:F ratio 7:3) and lacks characteristic response to immunosuppressants [62].

At this time, there is no established medical treatment for patients with PSC and elective liver transplant often represents the treatment of choice in advanced stages [63].

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4. <u>Viral Hepatitis</u>

<u>4.1 Hepatitis C</u>

The number of hepatitis C virus (HCV) cases is estimated to be about 160 million worldwide, with most of affected individuals being unaware [64]. The incidence, prevalence and male/female ratio of HCV infection and chronic hepatitis C (CHC) vary extremely, depending on the geographical area and likely reflecting cultural, behavioural and social differences influencing the risk of exposure, the timing of the first diagnosis and access to treatment [65].

The long-term prognosis of such infection is highly variable, and ranges from minimal histological changes to cirrhosis with potential development of hepatocellular carcinoma (HCC).

The proportion of subjects that spontaneously clear the virus after the infection ranges from 10 to 26%, with a high rate of chronicity expected [66, 67]. Female gender has been associated with higher rates of spontaneous viral clearance, symptomatic disease with jaundice and genetic polymorphisms of interleukin-28B (IL28B, also named IFN lambda-3, IFNL3) [68, 69].

A large study on 632 patients with acute HCV from different countries showed that spontaneous viral clearance was favourable predicted by IL28B CC genotype, HCV genotype 1 and female sex [70]. Also, the effect of IL28B CC genotype on clearance was greater, even if not statistically significant, among females than males, in consistency with a possible synergistic effect between IL28B CC genotype and female sex demonstrated by previous findings [71]. The potential interaction between female gender and Il28B polymorphism

might be explained by a mechanism involving the stimulation of toll like receptor 7 (TLR7), a receptor involved in recognition of viral products and activation of innate immunity, and a subsequent increase in IFN-α and IFN-λ responses.

The association between female gender and spontaneous viral clearance may also be partially explained by the sex-based differences in immunity, likely due to the direct influence of sexual hormones on immunological cells [72, 73].

Another study demonstrated a gender-dependent role for certain polymorphisms of CTLA4, an inhibitory T-cell receptor expressed on activated regulatory T-lymphocytes, in spontaneous or interferon-alpha-induced resolution of chronic hepatitis C virus infection [74], implying that gender-based differences in immunity response could influence the response to interferon treatment in patients with CHC.

Males with CHC have a two-fold greater progression rate to fibrosis compared with females, independently from alcohol intake [75]. The frequency of the IL-10 promoter GG genotype, associated to higher levels of interleukin 10, was tested in patients with HCV infection: female patients, who had an increased prevalence of such genotype, tended to develop CHC but had a lower risk of progression to cirrhosis [76].

Also, in an Italian gender-oriented analysis of CHC patients treated with pegylated-interferon and ribavirin, different predictive factors for SVR according to gender were found: SVR was independently associated with younger age and IL28B CC genotype in females, while absence of visceral obesity, HCV-RNA lower than 400 000 IU/mL and IL28B CC genotype were independently associated with SVR in males [77].

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Female sex was associated to a higher incidence of adverse events (i.e. anaemia) and the need for dose modification in retrospective studies on treatment of HCV with pegylated-interferon and ribavirin, but had the same SVR rate if compared with male sex [78].

As for the new direct acting antiviral (DAA) treatments, the SVR is usually reached in over 90% patients with HCV, independently of virus genotype, patient sex and liver disease stage, thus offering an unprecedented opportunity to cure hepatitis C virus (HCV) infection [79-81].

4.2 Hepatitis B

Hepatitis B virus (HBV) is an important cause of acute and chronic liver disease globally. Despite an encouraging decline in its incidence, likely attributable to effective vaccination programs especially in western countries, it is estimated that 240 million persons worldwide have chronic hepatitis B (CHB) with a geographically variable prevalence [82].

Chronic HBV infection is associated with hepatocellular necroinflammation and progression to hepatic fibrosis, and it is an independent recognised risk factor for hepatocellular carcinoma (HCC) development even in the absence of liver fibrosis [83].

A higher male prevalence among CHB carriers is established, as well as a gender-based disparity in HBV clearance, which is higher in HBV-infected females.

Furthermore, male sex is an independent predictor of liver disease severity among chronic HBsAg carriers, with males having a more rapid progression of liver disease, higher morbidity, HCC incidence and mortality if compared to females [84-86].

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Both control of the HBV-induced liver damage and immune clearance of HBV antigens are usually more quickly achieved in women, likely for the different regulation of immune cells from male and female sex hormones, as seen for HCV infection.

HBV is considered to be a sex hormone-responsive virus, differently regulated by hepatic androgen or hepatic estrogen axis. Indeed, it has been seen that, once stimulated, the androgen receptor (AR) actively binds to the androgen responsive elements (AREs) within HBV enhancer 1 leading to a subsequent increase of overall HBV mRNAs production [87]. On the other side, it has recently been provided that estrogen binding to hepatic estrogen receptor α (ERα) reduces overall HBV mRNA levels by suppressing the activity of viral enhancer 1 [88]. Moreover, stimulated ERα passively represses HBV transcription by interacting with hepatocyte nuclear factor 4α (HNF-4α) and preventing its binding to viral enhancer 1 [89].

The greater rate of hepatic fibrosis progression seen in men may be due to a lower production of estradiol, an estrogen hormone but also an endogenous antioxidant that reduces redox hepatocellular apoptosis and hepatic stellate cells (HSC) activation by decreasing reactive oxygen species generation, thus suppressing hepatic fibrosis in animal models [90].

5. **Metabolic liver disease**

5.1 Hereditary Hemochromatosis (HH)

Hemochromatosis is a clinical syndrome caused by the toxic effects of excessive iron deposition in parenchymatous organs, nowadays recognised as due to partial or total loss of

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activity of hepcidin, a liver-synthetized hormone that prevents unneeded iron from entering the bloodstream by regulating its absorption [91].

There are different types of hereditary hemochromatosis (HH): type 1 or classic HH, type 2 or juvenile hemochromatosis, type 3 and type 4 or ferroportin disease [92, 93]. Type 1 HH, by far the most common form, is highly prevalent in the Caucasian population and mainly caused by the homozygous mutation C282Y or by compound heterozygous mutations C282Y/H63D of the HFE gene [94]. The HFE gene encodes for a protein involved in the signalling pathway of iron status to hepcidin [95] and the loss of HFE function leads to inappropriately low hepcidin levels and iron overload [96].

Type 1 HH is typically an adult-onset disease with incomplete penetrance and genetic testing is usually recommended for those individuals who have iron overload or a family history positive for HFE-associated HH [97]. Therefore, many cases of HH are diagnosed before the onset of clinical symptoms.

Symptoms of HH usually appear in the fifth decade of age and include weakness, hepatomegaly, darkened skin and joint pain and overall the clinical severity is mild. If untreated, affected patients are at high risk of heart disease, endocrine dysfunctions and liver cirrhosis [98].

HH is not a gender-specific disease, but affected males tend to present symptoms earlier than females and this can be explained by the protective effect of the menstrual cycle in women. Male patients with hemochromatosis tend to have higher ferritin levels, accumulate more iron and have a higher incidence of liver injury and progression to fibrosis,

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requiring treatment with phlebotomy to be started earlier from the time of the diagnosis, if compared with female subjects [99].

Also, symptoms of hypogonadism can be more evident in men, including erectile dysfunction, loss of secondary sexual characters, and infertility [100].

5.2 Non-alcoholic fatty liver disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) is nowadays the most common cause of deranged hepatic function tests in western countries [101]. Its prevalence is widely variable and reaches 20-30% in Europe, Japan and US [102]. NAFLD is generally associated with obesity, insulin resistance and visceral adiposity, and it is considered to be the hepatic manifestation of the Metabolic Syndrome (MetS) [103].

Histologically, NAFLD extends from simple steatosis to steatohepatitis, fibrosis and cirrhosis and a prompt diagnosis, particularly of steatohepatitis and fibrosis at an early stage, is important in order to identify those patients who should undergo a stricter follow-up, interventions aiming at weight reduction, treatment of the other components of the metabolic syndrome and inclusion in trials for new therapeutic strategies [104].

There are conflicting data in the literature about gender-based difference in NAFLD prevalence and prognosis. Despite being initially considered a female disease [105], recent cross-sectional studies have shown that NAFLD is as common in men as in women [106]. Others have reported a higher prevalence of advanced disease among women, and therefore identified female sex as a risk factor for liver disease progression in NAFLD [107]. A recent review on the prevalence, gender and ethnic variations and prognosis of NAFLD in the Japanese population, pointed out that among younger patients both NAFLD and NASH

are more common in men while after 60 years of age, the prevalence of NASH is higher in women [108]. This may imply a protective role of endogenous estrogens in NASH, as seen for other liver diseases, against oxidative stress damage. Furthermore, estrogens promote accumulation of fat in the gluteo-femoral region and, conversely, their loss during menopause is associated with an increase in central fat and visceral adipose tissue, both recognised as negative predictive factors for development and progression of NAFLD [109]. Another cross-sectional study involving 1170 community-based Australian adolescents showed that females had a significantly higher prevalence of NAFLD (16.3% versus 10.1%) and central obesity (33.2% versus 9.9%) while male phenotype of NAFLD was associated with more adverse metabolic features and a greater visceral adiposity [110]. These data suggest that more aggressive strategies should be offered to men of all ages with NAFLD, in order to address the higher rates of deranged behavioural habits and concomitant metabolic diseases, and to peri /post-menopausal women with NAFLD, who are at high risk of disease progression and cardiovascular comorbidities after the loss of estrogen protective effect.

Definitive data are lacking, but a possible role for estrogenic treatment in postmenopausal women with NAFLD is emerging, also supported by the improvement of liver function tests seen in post-menopausal women taking estrogenic replacement therapy and by the observed association of NAFLD with the anti-estrogen tamoxifen [111, 112].

6. <u>Vascular liver disease</u>

Vascular liver disease encompasses a spectrum of diseases like Budd-Chiari syndrome (BCS), portal vein thrombosis, idiopathic non-cirrhotic portal hypertension, sinusoidal obstruction syndrome and hereditary haemorrhagic telangiectasia.

BCS is a rare disorder featured by venous flow obstruction at the suprahepatic level, usually caused by a combination of thrombogenic conditions and triggering factors. Epidemiologically, BCS is overall more common in males compared to females (1.5:1), with a distinction linked to the variant: isolated hepatic vein thrombosis, more commonly seen in Western countries, has a higher female prevalence, while combined hepatic-inferior cava vein thrombosis is more commonly seen in Eastern male patients[113, 114]. Females have higher rates of acute presentation of the disease and a greater probability to be managed by anticoagulation only.

The management remains similar in non-pregnant women and men, except for oral contraceptive (OC) therapy, which is a well-recognised additional risk factor for BCS in women that therefore needs to be investigated and stopped [115]. There is no difference in the recommended level of anticoagulation and interventional radiological procedures among both genders, with a risk of bleeding on anticoagulation that appears to be similar for both genders [116].

According to a recent systematic review and meta-analysis, pregnancy-related BCS has a prevalence that varies from 0 to 21.5% (pooled prevalence between 6.7 and 7.3 %), and it can present with acute fulminant liver failure due to occlusion of all three hepatic veins during pregnancy or puerperium [117]. Particularly, women with protein S deficiency seem at higher risk for developing BCS during pregnancy [118].

Hereditary haemorrhagic telangiectasia is a rare genetic condition that affects the liver by the development of venous malformations (VMs). Previous data show a strong and significant predominance of hepatic VMs in females who have HHT, both for asymptomatic and symptomatic lesions, with a male : female ratio varying from 1:2 to 1:4.5 [119].

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OC therapy is an acquired risk factor for other vascular disorders in women: particularly, hepatic sinusoidal dilatation and hepatic peliosis are classic complications of long-term use of OCs [120].

7. Neoplasms of the liver

7.1 Benign Hepatic Lesions

Several benign liver tumours are more common in women. Benign liver lesions that predominantly occur in women include cavernous haemangioma, focal nodular hyperplasia (FNH), hepatic adenoma, biliary cystadenoma and solitary hepatic cysts. Estrogens are associated to benign liver tumours, likely for an increase of hormonal receptors expression and estrogens-stimulated hepatocellular replication in such lesions, although the exact mechanisms are still unclear.

Hemangioma is the most common, with an estimated prevalence of 5% in imaging series and of 20% in autopsy series and a variable female to male gender ratio (between 1.2:1 and 6:1) [121]. It is usually diagnosed incidentally because asymptomatic, and it is managed conservatively, with no gender disparity in most cases. Oral contraceptives and pregnancy are usually not contraindicated, although rare cases of development of Kasabach–Merritt syndrome, a potentially life-threatening coagulopathy characterized by enlarging hemangioma and thrombocytopenia, usually associated with kaposiform hemangioendothelioma (KHE), tufted angiomas and rarely with congenital hemangiomas, have been described in pregnant women with liver hemangiomas larger than 5 cm [119].

FNH has a prevalence ranging between 0.4% and 3%, with a strong female preponderance (90 % of cases) [122]. However, there is no discrepancy in the histological features, the natural history and the management of FNH according to gender. For a typical FNH lesion, follow-up is not necessary unless there is underlying vascular liver disease, and surgical

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treatment is usually pursued in exceptional cases (pedunculated, expanding, exophytic lesions). There is no indication for discontinuing OCs and follow-up during pregnancy is not necessary [121].

Adenomas are monoclonal tumours that are defined as HNF1-α type, inflammatory type, Beta-catenin type and unclassified. Females have mainly the first two types of adenoma, usually associated with a better prognosis.

Hepatic adenomas were rarely reported before the advent of OCs and multiple studies carried out thereafter have confirmed an association between the development of hepatic adenomas with the dose and duration of hormonal therapy, with a higher risk of development in women over the age of 30 years who have been using OCs for longer than 25 months, likely due to the effect of estrogens on hepatocytes [123-125]. The annual incidence is approximately 1 per million in women who have never used OCs compared with 30 to 40 per million in long-term users [126]. Additionally, adenomas are more numerous, larger, and more likely to bleed in patients who take OCs. Regression of adenomas has been observed after discontinuation of OCs with recurrence during readministration or pregnancy [127-129]. Therefore, all females are advocated to stop using OCs after the diagnosis of adenoma.

In male patients all adenomas are to be resected, while in females only those larger than 5 cm or proved to be enlarging on the sequential scan are to be resected.

Emerging understanding of the FNH and adenomas pathogenesis points out that males are more predisposed to develop adenomas with beta-catenin activation, while females appear to have the inactivation of a gene involved in estrogen metabolism (CYP1B1) and a consequent higher rate of the HNF1-α subtype of adenomas [130] . Inactivating mutations

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of HNF1-α (a human tumour suppressor gene) was found in 35% to 50% of hepatic adenomas [131].

7.2 Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma (HCC) is the third most common cause of death from cancer worldwide and it is notably more prevalent in males in most of the published studies, with reported male to female ratios ranging from 2:1 to 8:1 [132].

The reasons for sex differences in the incidence of HCC are still unclear. Considering that this gender disparity is quite significant for pre-menopausal women, a protective role of estrogen towards HCC development has been postulated. Furthermore, studies have demonstrated that androgen/androgen-receptor (AR) signalling has an important role in cancer initiation [133, 134] while it seems to suppress metastasis of HCC, exerting a suppressive effect on the progression of late-stage HCC [135]. Nevertheless, the association between increasing levels of testosterone or anabolic hormones and development of HCC remains controversial [136-139].

Women are usually diagnosed with HCC at a significantly older age than men and are also more likely to be diagnosed by screening methods at an earlier, asymptomatic stage of disease, with fewer and smaller tumours [140, 141]. However, when diagnosed after symptomatic presentation they tend to have a diffuse infiltrating variety of HCC and a more advanced stage of the disease [141-145].

Overall, females are either equal or more likely to undergo therapeutic curative procedures, including surgical resection (lobar/segmental), transplantation or radiofrequency ablation [141, 142, 146].

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Even when compared to males undergoing surgical resection, female patients tend to have higher tumour encapsulation, lower tumour microsatellites, lower liver invasion, lower incidence of tumour recurrence [147] and more favourable actuarial survival.

Males are more likely to undergo non-curative systemic therapy and male sex is considered to be an independent risk factor for poor outcome of HCC [141, 142].

Sorafenib is a multikinase inhibitor approved for treatment of patients with advanced hepatocellular carcinoma who have compensated liver function (class Child-Pugh A) but are not candidates for potentially curative treatment or trans-arterial chemoembolization [148]. In studies on sorafenib pharmacokinetics and pharmacodynamics, gender was the sole parameter independently associated with sorafenib exposure, with a greater absolute AUC in females than in males [149] and a likely synergism between sorafenib and estrogens in terms of anti-HCC activity [150]. Female gender is a better prognostic factor either in resectable either in unresectable HCC, with an increased overall survival [145, 151].

Table 1. Gender-based differences in liver diseases

Liver disease	M : F	Female	Male
DILI	1 1.5	- More frequent presentation with/progression to ALF - Hepatitis type	Higher incidence of chronic liver injury type
ALD	1.5-2 1	- Lower alcohol toxic threshold - Faster progression to liver fibrosis	
AIH	1 7-9	Different response to therapy?	
PBC	1 10	Pruritus as first symptom	-Presentation at an older age with more severe disease

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				- Non-response to UDCA
PSC		7 3		
HCV		Variable M > F	- Higher rate of spontaneous viral clearance - Presentation at a younger age, with jaundice - Higher prevalence of IL28BCC polymorphism - Higher incidence of adverse events, i.e. anaemia, on PEG-IFN/RBV	Greater progression rate to liver fibrosis
HBV		Variable M > F	Quicker control of HBV-induced liver damage	- Lower HBV clearance - Rapid progression of liver disease - Higher morbidity, HCC incidence and mortality
HH		M ~ F		- Earlier presentation - Higher ferritin - Higher incidence of liver injury - More evident hypogonadism
NAFLD		Contrasting data	Increased incidence after menopause	
BENIGN VASCULAR LESIONS	BCS	1.5 1	- Isolated hepatic vein thrombosis - OCP-associated risk - Higher rates of acute presentation - More often managed by anticoagulation only	- Combined hepatic-inferior cava veins thrombosis
	HHT	1 2-4.5		
BENIGN LESIONS	Adenoma	1 10	- Higher prevalence of HNF1-α subtype - Strong association	Higher prevalence of Beta-catenin activation

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			with OCPs	
FNH	1	9		
HCC	2-8	1	- Better response to Sorafenib - Increased overall survival	Higher risk for poor outcome of HCC

Abbreviations: DILI, drug-induced liver disease; ALF, acute liver failure ; ALD, alcoholic liver disease; AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; UDCA, u ursodeoxycholic acid; PSC, primary sclerosing cholangitis; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; RBV, ribavirin;   HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HH, hereditary hemochromatosis; NAFLD, non-alcoholic liver disease; BCS, Budd-Chiari syndrome; OCP, oral contraceptive pill; HHT, hereditary haemorrhagic telangiectasia; HMG, hemangioma; FNH, focal nodular hyperplasia.

8.   Advanced liver disease and cirrhosis

Male patients with chronic liver disease tend to have a faster progression of liver fibrosis compared to women except for ALD [152] patients (Table 1).

Cirrhotic patients are more often males with underlying viral and/or alcoholic liver disease [153-155], while women represent less than 40% of all patients with cirrhosis in the Western countries, with autoimmune hepatitis and primary biliary cirrhosis as main underlying aetiology [156, 157].

Such favourable effect of the female sex relies on many factors, as already mentioned in the sections dedicated to the specific liver diseases: a lower risk of iron overload, a lower prevalence of viral infections and overweight, a lower alcohol and tobacco consumption and

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a positive influence of estrogens and/or estrogen receptors pathways on fibrogenesis, the latter explaining the gradual increase in morbidity after the onset of menopause.

The incidence of decompensation events, such as variceal haemorrhage, development of hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis and their management is usually similar in both sexes and related to the liver disease stage, but some differences in natural history, manifestations and mortality risk may encourage a gender-based approach to counselling and follow-up.

Hypogonadism is a common finding in patients with liver cirrhosis. Altered albumin synthesis secondary to malnutrition, reduced clearance of sex hormones, systemic toxaemia and altered antero-pituitary hormone secretion (sometimes aggravated by metabolic damage from toxic causes as in ALD or HH) are the main culprits.

Clinical signs related with hypogonadism in cirrhotic men (abnormal distribution of fat and gynaecomastia, testicular and prostatic atrophy, decreased libido, erectile dysfunction and infertility[158, 159]) are mainly caused by low serum testosterone and high estrogen levels and often exacerbated by the introduction of spironolactone [160, 161]. Testosterone deficiency has been identified as an independent prognostic marker in cirrhosis [162].

Typical signs of hypogonadism in cirrhotic women are loss of secondary sexual characteristics, anovulation, amenorrhoea and infertility due to lower levels of total testosterone and higher levels of prolactin and delta-4-androstenedione [161, 163]. In the presence of compensated cirrhosis and mild portal hypertension, regular menstrual circle is preserved and hormonal replacement therapy is not contraindicated.

Pregnancy is a rare event in patients with cirrhosis. Despite the exact incidence is unknown, maternal mortality and pregnancy outcome have likely improved along with advancements in the treatment of specific liver diseases and in the management of portal hypertension and variceal haemorrhage [164]. Further studies are required of specific treatment with gonadal hormone replacement in patients with liver cirrhosis.

Hypogonadism can also worsen clinical manifestations of advanced liver disease such as sarcopenia and bone disease.

Malnutrition is one of the most common complications in cirrhosis and it leads, in the majority of cases, to a chronic catabolic state with consumption of amino acids and sarcopenia [165] . Male sex has been found to be a predictor for sarcopenia and this could be linked to the abundance of fat stores in women, even in advanced stages of liver disease, and to a different, sex hormone-dependant, pattern of skeletal muscle turnover [166] .

Patients with cirrhosis should be screened for osteoporosis irrespective of gender. Nevertheless, since female sex, advanced age, chronic cholestasis and long-term use of steroid therapy are independent risk factors for osteoporosis, the prevalence of osteoporosis tends to be higher in cirrhotic postmenopausal patients [167, 168]. Bisphosphonates are the agents of choice for the treatment of hepatic osteoporosis, and hormone replacement therapy can be an option for post-menopausal cirrhotic females [168].

Porto-pulmonary hypertension (PPHTN), a possible complication of liver cirrhosis, develops more often in female patients compared to males, however the treatment is the same [169, 170].

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Overall, males are two-fold more likely of being hospitalized and dying of liver cirrhosis than females [155, 171].

Women have lower rate of progression to end-stage liver disease and better long-term post-transplant survival, although female sex seemed to be associated to a worst outcome in case of HCV reactivation after liver transplant , at least in the pre-DAAs era [172]. Female sex is also a predictor of mortality on liver transplant waiting list and the disparity in the female/male liver transplant rates has particularly increased after the introduction of the Model for the End-stage Liver Disease (MELD) Score to assess and stratify patients with advanced liver disease [173] [174]. This could be due either to the reduced muscle mass in women, therefore lower average levels of creatinine (one of the components of the MELD Score) either to the difficulty of finding an appropriately sized graft.

Conclusions

Gender variations in prevalence, incidence, manifestations and outcomes prevail in common liver diseases, and such differences are important to identify as they influence the likelihood of a given diagnosis for a patient, the potential for progression of the liver disease and the preventive as well the therapeutic strategies.

During the last decades, basic scientific and clinical research has been proved to be gender unbalanced, with female subjects traditionally underrepresented.

Therefore, a renewed attention on a more gender-specific approach to hepatology and medicine in general is required and the efforts of the scientific community should be addressed towards a better understanding of the mechanisms underlying such differences, likely centred on differing behavioural, hormonal and immune factors.

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References

[1] G.D. Anderson, Gender differences in pharmacological response, Int Rev Neurobiol 83 (2008) 1-10.

[2] G. Baggio, A. Corsini, A. Floreani, S. Giannini, V. Zagonel, Gender medicine: a task for the third millennium, Clin Chem Lab Med 51(4) (2013) 713-27.

[3] D.L. Ahlbory-Dieker, B.D. Stride, G. Leder, J. Schkoldow, S. Trolenberg, H. Seidel, C. Otto, A. Sommer, M.G. Parker, G. Schutz, T.M. Wintermantel, DNA binding by estrogen receptor-alpha is essential for the transcriptional response to estrogen in the liver and the uterus, Mol Endocrinol 23(10) (2009) 1544-55.

31

[4] D.J. Waxman, M.G. Holloway, Sex differences in the expression of hepatic drug metabolizing enzymes, Mol Pharmacol 76(2) (2009) 215-28.

[5] D.E. Amacher, Female gender as a susceptibility factor for drug-induced liver injury, Hum Exp Toxicol 33(9) (2014) 928-39.

[6] G.D. Anderson, Sex and racial differences in pharmacological response: where is the evidence? Pharmacogenetics, pharmacokinetics, and pharmacodynamics, J Womens Health (Larchmt) 14(1) (2005) 19-29.

[7] T.J. Nicolson, H.R. Mellor, R.R. Roberts, Gender differences in drug toxicity, Trends Pharmacol Sci 31(3) (2010) 108-14.

[8] M.H. Court, Interindividual variability in hepatic drug glucuronidation: studies into the role of age, sex, enzyme inducers, and genetic polymorphism using the human liver bank as a model system, Drug Metab Rev 42(1) (2010) 209-24.

[9] C.M. Hunt, W.R. Westerkam, G.M. Stave, Effect of age and gender on the activity of human hepatic CYP3A, Biochem Pharmacol 44(2) (1992) 275-83.

[10] W.M. Lee, Drug-induced hepatotoxicity, N Engl J Med 349(5) (2003) 474-85.

[11] C. Sgro, F. Clinard, K. Ouazir, H. Chanay, C. Allard, C. Guilleminet, C. Lenoir, A. Lemoine, P. Hillon, Incidence of drug-induced hepatic injuries: a French population-based study, Hepatology 36(2) (2002) 451-5.

[12] E.S. Bjornsson, O.M. Bergmann, H.K. Bjornsson, R.B. Kvaran, S. Olafsson, Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland, Gastroenterology 144(7) (2013) 1419-25, 1425 e1-3; quiz e19-20.

[13] N.P. Chalasani, P.H. Hayashi, H.L. Bonkovsky, V.J. Navarro, W.M. Lee, R.J. Fontana, G. Practice Parameters Committee of the American College of, ACG Clinical Guideline: the

32

diagnosis and management of idiosyncratic drug-induced liver injury, Am J Gastroenterol 109(7) (2014) 950-66; quiz 967.

[14] K. Fisher, R. Vuppalanchi, R. Saxena, Drug-Induced Liver Injury, Arch Pathol Lab Med 139(7) (2015) 876-87.

[15] N. Chalasani, H.L. Bonkovsky, R. Fontana, W. Lee, A. Stolz, J. Talwalkar, K.R. Reddy, P.B. Watkins, V. Navarro, H. Barnhart, J. Gu, J. Serrano, N. United States Drug Induced Liver Injury, Features and Outcomes of 899 Patients With Drug-Induced Liver Injury: The DILIN Prospective Study, Gastroenterology 148(7) (2015) 1340-52 e7.

[16] J.G. Stine, N. Chalasani, Chronic liver injury induced by drugs: a systematic review, Liver Int 35(11) (2015) 2343-53.

[17] S. Chitturi, G.C. Farrell, Drug-induced cholestasis, Semin Gastrointest Dis 12(2) (2001) 113-24.

[18] D.E. Kleiner, N.P. Chalasani, W.M. Lee, R.J. Fontana, H.L. Bonkovsky, P.B. Watkins, P.H. Hayashi, T.J. Davern, V. Navarro, R. Reddy, J.A. Talwalkar, A. Stolz, J. Gu, H. Barnhart, J.H. Hoofnagle, N. Drug-Induced Liver Injury, Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations, Hepatology 59(2) (2014) 661-70.

[19] K. Fattinger, M. Roos, P. Vergeres, C. Holenstein, B. Kind, U. Masche, D.N. Stocker, S. Braunschweig, G.A. Kullak-Ublick, R.L. Galeazzi, F. Follath, T. Gasser, P.J. Meier, Epidemiology of drug exposure and adverse drug reactions in two swiss departments of internal medicine, Br J Clin Pharmacol 49(2) (2000) 158-67.

[20] J. Cho, L. Kim, Z. Li, N.R. Rose, M.V. Talor, D.B. Njoku, Sex bias in experimental immune-mediated, drug-induced liver injury in BALB/c mice: suggested roles for Tregs, estrogen, and IL-6, PLoS One 8(4) (2013) e61186.

[21] Y. Toyoda, T. Miyashita, S. Endo, K. Tsuneyama, T. Fukami, M. Nakajima, T. Yokoi, Estradiol and progesterone modulate halothane-induced liver injury in mice, Toxicol Lett 204(1) (2011) 17-24.

[22] M. Chen, A. Suzuki, J. Borlak, R.J. Andrade, M.I. Lucena, Drug-induced liver injury: Interactions between drug properties and host factors, J Hepatol 63(2) (2015) 503-14.

[23] L. Du, H. Bayir, Y. Lai, X. Zhang, P.M. Kochanek, S.C. Watkins, S.H. Graham, R.S. Clark, Innate gender-based proclivity in response to cytotoxicity and programmed cell death pathway, J Biol Chem 279(37) (2004) 38563-70.

[24] D. Pessayre, D. Larrey, Drug-Induced Liver Injury, in: J.-P.B. J. Rodés, A. T. Blei, J. Reichen and M. Rizzetto (Ed.), Textbook of Hepatology: From Basic Science to Clinical Practice, Blackwell Publishing Ltd, Oxford, UK, 2008.

[25] R.J. Andrade, M.I. Lucena, M.C. Fernandez, G. Pelaez, K. Pachkoria, E. Garcia-Ruiz, B. Garcia-Munoz, R. Gonzalez-Grande, A. Pizarro, J.A. Duran, M. Jimenez, L. Rodrigo, M. Romero-Gomez, J.M. Navarro, R. Planas, J. Costa, A. Borras, A. Soler, J. Salmeron, R. Martin-Vivaldi, D. Spanish Group for the Study of Drug-Induced Liver, Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period, Gastroenterology 129(2) (2005) 512-21.

[26] A.M. Larson, J. Polson, R.J. Fontana, T.J. Davern, E. Lalani, L.S. Hynan, J.S. Reisch, F.V. Schiodt, G. Ostapowicz, A.O. Shakil, W.M. Lee, G. Acute Liver Failure Study, Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study, Hepatology 42(6) (2005) 1364-72.

[27] W.M. Lee, R.H. Squires, Jr., S.L. Nyberg, E. Doo, J.H. Hoofnagle, Acute liver failure: Summary of a workshop, Hepatology 47(4) (2008) 1401-15.

34

[28] P. Mathurin, R. Bataller, Trends in the management and burden of alcoholic liver disease, J Hepatol 62(1 Suppl) (2015) S38-46.

[29] R.W. Wilsnack, S.C. Wilsnack, A.F. Kristjanson, N.D. Vogeltanz-Holm, G. Gmel, Gender and alcohol consumption: patterns from the multinational GENACIS project, Addiction 104(9) (2009) 1487-500.

[30] A. Erol, V.M. Karpyak, Sex and gender-related differences in alcohol use and its consequences: Contemporary knowledge and future research considerations, Drug Alcohol Depend 156 (2015) 1-13.

[31] P.K. Eagon, Alcoholic liver injury: influence of gender and hormones, World J Gastroenterol 16(11) (2010) 1377-84.

[32] S. Bellentani, G. Saccoccio, G. Costa, C. Tiribelli, F. Manenti, M. Sodde, L. Saveria Croce, F. Sasso, G. Pozzato, G. Cristianini, G. Brandi, Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group, Gut 41(6) (1997) 845-50.

[33] R.S. O'Shea, S. Dasarathy, A.J. McCullough, D. Practice Guideline Committee of the American Association for the Study of Liver, G. Practice Parameters Committee of the American College of, Alcoholic liver disease, Hepatology 51(1) (2010) 307-28.

[34] L. European Association for the Study of, EASL clinical practical guidelines: management of alcoholic liver disease, J Hepatol 57(2) (2012) 399-420.

[35] U. Becker, A. Deis, T.I. Sorensen, M. Gronbaek, K. Borch-Johnsen, C.F. Muller, P. Schnohr, G. Jensen, Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study, Hepatology 23(5) (1996) 1025-9.

[36] A.A. Nanji, G.L. Su, M. Laposata, S.W. French, Pathogenesis of alcoholic liver disease--recent advances, Alcohol Clin Exp Res 26(5) (2002) 731-6.

35

[37] J. Rehm, B. Taylor, S. Mohapatra, H. Irving, D. Baliunas, J. Patra, M. Roerecke, Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis, Drug Alcohol Rev 29(4) (2010) 437-45.

[38] M. Frezza, C. di Padova, G. Pozzato, M. Terpin, E. Baraona, C.S. Lieber, High blood alcohol levels in women. The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism, N Engl J Med 322(2) (1990) 95-9.

[39] C. Muller, Liver, alcohol and gender, Wien Med Wochenschr 156(19-20) (2006) 523-6.

[40] K. Ikejima, N. Enomoto, Y. Iimuro, A. Ikejima, D. Fang, J. Xu, D.T. Forman, D.A. Brenner, R.G. Thurman, Estrogen increases sensitivity of hepatic Kupffer cells to endotoxin, Am J Physiol 274(4 Pt 1) (1998) G669-76.

[41] F. Alvarez, P.A. Berg, F.B. Bianchi, L. Bianchi, A.K. Burroughs, E.L. Cancado, R.W. Chapman, W.G. Cooksley, A.J. Czaja, V.J. Desmet, P.T. Donaldson, A.L. Eddleston, L. Fainboim, J. Heathcote, J.C. Homberg, J.H. Hoofnagle, S. Kakumu, E.L. Krawitt, I.R. Mackay, R.N. MacSween, W.C. Maddrey, M.P. Manns, I.G. McFarlane, K.H. Meyer zum Buschenfelde, M. Zeniya, et al., International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis, J Hepatol 31(5) (1999) 929-38.

[42] L. European Association for the Study of the, EASL Clinical Practice Guidelines: Autoimmune hepatitis, J Hepatol 63(4) (2015) 971-1004.

[43] M.P. Manns, A.J. Czaja, J.D. Gorham, E.L. Krawitt, G. Mieli-Vergani, D. Vergani, J.M. Vierling, D. American Association for the Study of Liver, Diagnosis and management of autoimmune hepatitis, Hepatology 51(6) (2010) 2193-213.

[44] P.T. Donaldson, D.G. Doherty, K.M. Hayllar, I.G. McFarlane, P.J. Johnson, R. Williams, Susceptibility to autoimmune chronic active hepatitis: human leukocyte antigens DR4 and A1-B8-DR3 are independent risk factors, Hepatology 13(4) (1991) 701-6.

[45] Y.S. de Boer, N.M. van Gerven, A. Zwiers, B.J. Verwer, B. van Hoek, K.J. van Erpecum, U. Beuers, H.R. van Buuren, J.P. Drenth, J.W. den Ouden, R.C. Verdonk, G.H. Koek, J.T. Brouwer, M.M. Guichelaar, J.M. Vrolijk, G. Kraal, C.J. Mulder, C.M. van Nieuwkerk, J. Fischer, T. Berg, F. Stickel, C. Sarrazin, C. Schramm, A.W. Lohse, C. Weiler-Normann, M.M. Lerch, M. Nauck, H. Volzke, G. Homuth, E. Bloemena, H.W. Verspaget, V. Kumar, A. Zhernakova, C. Wijmenga, L. Franke, G. Bouma, G. Dutch Autoimmune Hepatitis Study, S. LifeLines Cohort, P. Study of Health in, Genome-wide association study identifies variants associated with autoimmune hepatitis type 1, Gastroenterology 147(2) (2014) 443-52 e5.

[46] G. Toda, M. Zeniya, F. Watanabe, M. Imawari, K. Kiyosawa, M. Nishioka, T. Tsuji, M. Omata, Present status of autoimmune hepatitis in Japan--correlating the characteristics with international criteria in an area with a high rate of HCV infection. Japanese National Study Group of Autoimmune Hepatitis, J Hepatol 26(6) (1997) 1207-12.

[47] A.J. Czaja, M.D. Strettell, L.J. Thomson, P.J. Santrach, S.B. Moore, P.T. Donaldson, R. Williams, Associations between alleles of the major histocompatibility complex and type 1 autoimmune hepatitis, Hepatology 25(2) (1997) 317-23.

[48] A.J. Czaja, H.A. Carpenter, P.J. Santrach, S.B. Moore, Significance of HLA DR4 in type 1 autoimmune hepatitis, Gastroenterology 105(5) (1993) 1502-7.

[49] A.J. Czaja, P.T. Donaldson, Gender effects and synergisms with histocompatibility leukocyte antigens in type 1 autoimmune hepatitis, Am J Gastroenterol 97(8) (2002) 2051-7.

[50] T. Al-Chalabi, J.A. Underhill, B.C. Portmann, I.G. McFarlane, M.A. Heneghan, Impact of gender on the long-term outcome and survival of patients with autoimmune hepatitis, J Hepatol 48(1) (2008) 140-7.

[51] Y. Miyake, Y. Iwasaki, R. Terada, R. Okamaoto, H. Ikeda, Y. Makino, H. Kobashi, K. Takaguchi, K. Sakaguchi, Y. Shiratori, Persistent elevation of serum alanine aminotransferase

37

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levels leads to poor survival and hepatocellular carcinoma development in type 1 autoimmune hepatitis, Aliment Pharmacol Ther 24(8) (2006) 1197-205.

[52] A.J. Czaja, H.A. Carpenter, K.D. Lindor, Ursodeoxycholic acid as adjunctive therapy for problematic type 1 autoimmune hepatitis: a randomized placebo-controlled treatment trial, Hepatology 30(6) (1999) 1381-6.

[53] U. Nussinovitch, Y. Shoenfeld, The role of gender and organ specific autoimmunity, Autoimmun Rev 11(6-7) (2012) A377-85.

[54] E.J. Carey, A.H. Ali, K.D. Lindor, Primary biliary cirrhosis, Lancet 386(10003) (2015) 1565-75.

[55] A. Pares, L. Caballeria, J. Rodes, Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid, Gastroenterology 130(3) (2006) 715-20.

[56] C. Corpechot, O. Chazouilleres, R. Poupon, Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome, J Hepatol 55(6) (2011) 1361-7.

[57] V. Papastergiou, E.A. Tsochatzis, M. Rodriguez-Peralvarez, E. Thalassinos, G. Pieri, P. Manousou, G. Germani, C. Rigamonti, V. Arvaniti, S. Karatapanis, A.K. Burroughs, Biochemical criteria at 1 year are not robust indicators of response to ursodeoxycholic acid in early primary biliary cirrhosis: results from a 29-year cohort study, Aliment Pharmacol Ther 38(11-12) (2013) 1354-64.

[58] D.S. Smyk, E.I. Rigopoulou, A. Pares, C. Billinis, A.K. Burroughs, L. Muratori, P. Invernizzi, D.P. Bogdanos, Sex differences associated with primary biliary cirrhosis, Clin Dev Immunol 2012 (2012) 610504.

[59] M. Carbone, G.F. Mells, G. Pells, M.F. Dawwas, J.L. Newton, M.A. Heneghan, J.M. Neuberger, D.B. Day, S.J. Ducker, U.P. Consortium, R.N. Sandford, G.J. Alexander, D.E. Jones,

Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid, Gastroenterology 144(3) (2013) 560-569 e7; quiz e13-4.

[60] M.J. Pollheimer, E. Halilbasic, P. Fickert, M. Trauner, Pathogenesis of primary sclerosing cholangitis, Best Pract Res Clin Gastroenterol 25(6) (2011) 727-39.

[61] J.E. Eaton, J.A. Talwalkar, K.N. Lazaridis, G.J. Gores, K.D. Lindor, Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management, Gastroenterology 145(3) (2013) 521-36.

[62] R. Chapman, J. Fevery, A. Kalloo, D.M. Nagorney, K.M. Boberg, B. Shneider, G.J. Gores, D. American Association for the Study of Liver, Diagnosis and management of primary sclerosing cholangitis, Hepatology 51(2) (2010) 660-78.

[63] L. European Association for the Study of the, EASL Clinical Practice Guidelines: management of cholestatic liver diseases, J Hepatol 51(2) (2009) 237-67.

[64] D. Lavanchy, Evolving epidemiology of hepatitis C virus, Clin Microbiol Infect 17(2) (2011) 107-15.

[65] V. Liakina, S. Hamid, J. Tanaka, S. Olafsson, A.I. Sharara, S.M. Alavian, L. Gheorghe, E.S. El Hassan, F. Abaalkhail, Z. Abbas, A. Abdou, A. Abourached, F. Al Braiki, F. Al Hosani, K. Al Jaberi, M. Al Khatry, M.A. Al Mulla, H. Al Quraishi, A. Al Rifai, Y. Al Serkal, A. Alam, H.I. Alashgar, S. Alawadhi, L. Al-Dabal, P. Aldins, F.Z. Alfaleh, A.S. Alghamdi, R. Al-Hakeem, A.A. Aljumah, A. Almessabi, A.N. Alqutub, K.A. Alswat, I. Altraif, M. Alzaabi, N. Andrea, A.M. Assiri, M.A. Babatin, A. Baqir, M.T. Barakat, O.M. Bergmann, A.R. Bizri, S. Blach, A. Chaudhry, M.S. Choi, T. Diab, S. Djauzi, S. El Khoury, C. Estes, S. Fakhry, J.I. Farooqi, H. Fridjonsdottir, R.A. Gani, A. Ghafoor Khan, A. Goldis, M. Gottfredsson, S. Gregorcic, B. Hajarizadeh, K.H. Han, I. Hasan, A. Hashim, G. Horvath, B. Hunyady, R. Husni, W. Jafri, A. Jeruma, J.G. Jonasson, B. Karlsdottir, D.Y. Kim, Y.S. Kim, Z. Koutoubi, L.A. Lesmana, Y.S. Lim, A. Love, M.

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Maimets, M. Makara, R. Malekzadeh, M. Maticic, M.S. Memon, S. Merat, J.E. Mokhbat, F.H. Mourad, D.H. Muljono, A. Nawaz, N. Nugrahini, S. Priohutomo, H. Qureshi, P. Rassam, H. Razavi, D. Razavi-Shearer, K. Razavi-Shearer, B. Rozentale, M. Sadik, K. Saeed, A. Salamat, R. Salupere, F.M. Sanai, A. Sanityoso Sulaiman, R.A. Sayegh, J.D. Schmelzer, A. Sibley, M. Siddiq, A.M. Siddiqui, G. Sigmundsdottir, B. Sigurdardottir, D. Speiciene, A. Sulaiman, M.A. Sultan, M. Taha, H. Tarifi, G. Tayyab, I. Tolmane, M. Ud Din, M. Umar, J. Valantinas, J. Videcnik-Zorman, C. Yaghi, E. Yunihastuti, M.A. Yusuf, B.F. Zuberi, J. Gunter, Historical epidemiology of hepatitis C virus (HCV) in select countries - volume 3, J Viral Hepat 22 Suppl 4 (2015) 4-20.

[66] A.M. Di Bisceglie, Natural history of hepatitis C: its impact on clinical management, Hepatology 31(4) (2000) 1014-8.

[67] e.e.e. European Association for the Study of the Liver. Electronic address, EASL Recommendations on Treatment of Hepatitis C 2016, J Hepatol 66(1) (2017) 153-194.

[68] J.M. Micallef, J.M. Kaldor, G.J. Dore, Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies, J Viral Hepat 13(1) (2006) 34-41.

[69] N. Bulteel, P. Partha Sarathy, E. Forrest, A.J. Stanley, H. Innes, P.R. Mills, H. Valerio, R.N. Gunson, C. Aitken, J. Morris, R. Fox, S.T. Barclay, Factors associated with spontaneous clearance of chronic hepatitis C virus infection, J Hepatol 65(2) (2016) 266-72.

[70] J. Grebely, K. Page, R. Sacks-Davis, M.S. van der Loeff, T.M. Rice, J. Bruneau, M.D. Morris, B. Hajarizadeh, J. Amin, A.L. Cox, A.Y. Kim, B.H. McGovern, J. Schinkel, J. George, N.H. Shoukry, G.M. Lauer, L. Maher, A.R. Lloyd, M. Hellard, G.J. Dore, M. Prins, C.S.G. In, The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection, Hepatology 59(1) (2014) 109-20.

[71] C.H. van den Berg, B.P. Grady, J. Schinkel, T. van de Laar, R. Molenkamp, R. van Houdt, R.A. Coutinho, D. van Baarle, M. Prins, Female sex and IL28B, a synergism for spontaneous viral clearance in hepatitis C virus (HCV) seroconverters from a community-based cohort, PLoS One 6(11) (2011) e27555.

[72] S.L. Klein, A. Jedlicka, A. Pekosz, The Xs and Y of immune responses to viral vaccines, Lancet Infect Dis 10(5) (2010) 338-49.

[73] A. Bouman, M.J. Heineman, M.M. Faas, Sex hormones and the immune response in humans, Hum Reprod Update 11(4) (2005) 411-23.

[74] E. Schott, H. Witt, H. Hinrichsen, K. Neumann, V. Weich, A. Bergk, J. Halangk, T. Muller, S. Tinjala, G. Puhl, P. Neuhaus, B. Wiedenmann, T. Berg, Gender-dependent association of CTLA4 polymorphisms with resolution of hepatitis C virus infection, J Hepatol 46(3) (2007) 372-80.

[75] T. Poynard, P. Bedossa, P. Opolon, Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups, Lancet 349(9055) (1997) 825-32.

[76] N. Paladino, H. Fainboim, G. Theiler, T. Schroder, A.E. Munoz, A.C. Flores, O. Galdame, L. Fainboim, Gender susceptibility to chronic hepatitis C virus infection associated with interleukin 10 promoter polymorphism, J Virol 80(18) (2006) 9144-50.

[77] V. Di Marco, L. Covolo, V. Calvaruso, M. Levrero, M. Puoti, F. Suter, G.B. Gaeta, C. Ferrari, G. Raimondo, G. Fattovich, T. Santantonio, A. Alberti, R. Bruno, C. Mussini, M. Mondelli, F. Donato, A. Craxi, C. Multicenter Italian Group for the Study of Hepatitis, Who is more likely to respond to dual treatment with pegylated-interferon and ribavirin for chronic hepatitis C? A gender-oriented analysis, J Viral Hepat 20(11) (2013) 790-800.

[78] J.L. Narciso-Schiavon, L. Schiavon Lde, R.J. Carvalho-Filho, J.P. Sampaio, P.N. Batah, D.V. Barbosa, M.L. Ferraz, A.E. Silva, Gender influence on treatment of chronic hepatitis C genotype 1, Rev Soc Bras Med Trop 43(3) (2010) 217-23.

[79] N.L. Sussman, C.H. Remien, F. Kanwal, The end of hepatitis C, Clin Gastroenterol Hepatol 12(4) (2014) 533-6.

[80] N. Afdhal, S. Zeuzem, P. Kwo, M. Chojkier, N. Gitlin, M. Puoti, M. Romero-Gomez, J.P. Zarski, K. Agarwal, P. Buggisch, G.R. Foster, N. Brau, M. Buti, I.M. Jacobson, G.M. Subramanian, X. Ding, H. Mo, J.C. Yang, P.S. Pang, W.T. Symonds, J.G. McHutchison, A.J. Muir, A. Mangia, P. Marcellin, I.O.N. Investigators, Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection, N Engl J Med 370(20) (2014) 1889-98.

[81] P. Ferenci, D. Bernstein, J. Lalezari, D. Cohen, Y. Luo, C. Cooper, E. Tam, R.T. Marinho, N. Tsai, A. Nyberg, T.D. Box, Z. Younes, P. Enayati, S. Green, Y. Baruch, B.R. Bhandari, F.A. Caruntu, T. Sepe, V. Chulanov, E. Janczewska, G. Rizzardini, J. Gervain, R. Planas, C. Moreno, T. Hassanein, W. Xie, M. King, T. Podsadecki, K.R. Reddy, P.-I. Study, P.-I. Study, ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV, N Engl J Med 370(21) (2014) 1983-92.

[82] J.J. Ott, G.A. Stevens, J. Groeger, S.T. Wiersma, Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity, Vaccine 30(12) (2012) 2212-9.

[83] R.P. Beasley, L.Y. Hwang, C.C. Lin, C.S. Chien, Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22 707 men in Taiwan, Lancet 2(8256) (1981) 1129-33.

[84] D.S. Chen, Natural history of chronic hepatitis B virus infection: new light on an old story, J Gastroenterol Hepatol 8(5) (1993) 470-5.

42

[85] B.C. Taylor, J.M. Yuan, T.A. Shamliyan, A. Shaukat, R.L. Kane, T.J. Wilt, Clinical outcomes in adults with chronic hepatitis B in association with patient and viral characteristics: A systematic review of evidence, Hepatology 49(5 Suppl) (2009) S85-95.

[86] T. Stroffolini, R. Esvan, E. Biliotti, E. Sagnelli, G.B. Gaeta, P.L. Almasio, Gender differences in chronic HBsAg carriers in Italy: Evidence for the independent role of male sex in severity of liver disease, J Med Virol 87(11) (2015) 1899-903.

[87] S.H. Wang, S.H. Yeh, W.H. Lin, H.Y. Wang, D.S. Chen, P.J. Chen, Identification of androgen response elements in the enhancer I of hepatitis B virus: a mechanism for sex disparity in chronic hepatitis B, Hepatology 50(5) (2009) 1392-402.

[88] S.H. Wang, P.J. Chen, S.H. Yeh, Gender disparity in chronic hepatitis B: Mechanisms of sex hormones, J Gastroenterol Hepatol 30(8) (2015) 1237-45.

[89] S.H. Wang, S.H. Yeh, W.H. Lin, K.H. Yeh, Q. Yuan, N.S. Xia, D.S. Chen, P.J. Chen, Estrogen receptor alpha represses transcription of HBV genes via interaction with hepatocyte nuclear factor 4alpha, Gastroenterology 142(4) (2012) 989-998 e4.

[90] I. Shimizu, N. Kohno, K. Tamaki, M. Shono, H.W. Huang, J.H. He, D.F. Yao, Female hepatology: favorable role of estrogen in chronic liver disease with hepatitis B virus infection, World J Gastroenterol 13(32) (2007) 4295-305.

[91] A. Pietrangelo, Genetics, Genetic Testing, and Management of Hemochromatosis: 15 Years Since Hepcidin, Gastroenterology 149(5) (2015) 1240-1251 e4.

[92] C. Camaschella, A. Roetto, M. De Gobbi, Juvenile hemochromatosis, Semin Hematol 39(4) (2002) 242-8.

[93] A. Pietrangelo, The ferroportin disease, Blood Cells Mol Dis 32(1) (2004) 131-8.

[94] A. Pietrangelo, Hereditary hemochromatosis--a new look at an old disease, N Engl J Med 350(23) (2004) 2383-97.

[95] E. Corradini, C. Garuti, G. Montosi, P. Ventura, B. Andriopoulos, Jr., H.Y. Lin, A. Pietrangelo, J.L. Babitt, Bone morphogenetic protein signaling is impaired in an HFE knockout mouse model of hemochromatosis, Gastroenterology 137(4) (2009) 1489-97.

[96] K.R. Bridle, D.M. Frazer, S.J. Wilkins, J.L. Dixon, D.M. Purdie, D.H. Crawford, V.N. Subramaniam, L.W. Powell, G.J. Anderson, G.A. Ramm, Disrupted hepcidin regulation in HFE-associated haemochromatosis and the liver as a regulator of body iron homoeostasis, Lancet 361(9358) (2003) 669-73.

[97] E.P. Whitlock, B.A. Garlitz, E.L. Harris, T.L. Beil, P.R. Smith, Screening for hereditary hemochromatosis: a systematic review for the U.S. Preventive Services Task Force, Ann Intern Med 145(3) (2006) 209-23.

[98] P.C. Adams, Epidemiology and diagnostic testing for hemochromatosis and iron overload, Int J Lab Hematol 37 Suppl 1 (2015) 25-30.

[99] R.E. Fleming, R.S. Britton, A. Waheed, W.S. Sly, B.R. Bacon, Pathogenesis of hereditary hemochromatosis, Clin Liver Dis 8(4) (2004) 755-73, vii.

[100] D.D. Harrison-Findik, Gender-related variations in iron metabolism and liver diseases, World J Hepatol 2(8) (2010) 302-10.

[101] E.A. Tsochatzis, S. Manolakopoulos, G.V. Papatheodoridis, A.J. Archimandritis, Insulin resistance and metabolic syndrome in chronic liver diseases: old entities with new implications, Scandinavian journal of gastroenterology 44(1) (2009) 6-14.

[102] N. Chalasani, Z. Younossi, J.E. Lavine, A.M. Diehl, E.M. Brunt, K. Cusi, M. Charlton, A.J. Sanyal, The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology, Gastroenterology 142(7) (2012) 1592-609.

44

[103] E. Buzzetti, M. Pinzani, E.A. Tsochatzis, The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD), Metabolism 65(8) (2016) 1038-48.

[104] V. Papastergiou, E. Tsochatzis, A.K. Burroughs, Non-invasive assessment of liver fibrosis, Annals of gastroenterology : quarterly publication of the Hellenic Society of Gastroenterology 25(3) (2012) 218-231.

[105] A.J. Sanyal, A. American Gastroenterological, AGA technical review on nonalcoholic fatty liver disease, Gastroenterology 123(5) (2002) 1705-25.

[106] S.R. Weston, W. Leyden, R. Murphy, N.M. Bass, B.P. Bell, M.M. Manos, N.A. Terrault, Racial and ethnic distribution of nonalcoholic fatty liver in persons with newly diagnosed chronic liver disease, Hepatology 41(2) (2005) 372-9.

[107] B.A. Neuschwander-Tetri, S.H. Caldwell, Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference, Hepatology 37(5) (2003) 1202-19.

[108] E. Hashimoto, K. Tokushige, Prevalence, gender, ethnic variations, and prognosis of NASH, J Gastroenterol 46 Suppl 1 (2011) 63-9.

[109] H. Volzke, S. Schwarz, S.E. Baumeister, H. Wallaschofski, C. Schwahn, H.J. Grabe, T. Kohlmann, U. John, M. Doren, Menopausal status and hepatic steatosis in a general female population, Gut 56(4) (2007) 594-5.

[110] O.T. Ayonrinde, J.K. Olynyk, L.J. Beilin, T.A. Mori, C.E. Pennell, N. de Klerk, W.H. Oddy, P. Shipman, L.A. Adams, Gender-specific differences in adipose distribution and adipocytokines influence adolescent nonalcoholic fatty liver disease, Hepatology 53(3) (2011) 800-9.

[111] S. Bruno, P. Maisonneuve, P. Castellana, N. Rotmensz, S. Rossi, M. Maggioni, M. Persico, A. Colombo, F. Monasterolo, D. Casadei-Giunchi, F. Desiderio, T. Stroffolini, V. Sacchini, A. Decensi, U. Veronesi, Incidence and risk factors for non-alcoholic

steatohepatitis: prospective study of 5408 women enrolled in Italian tamoxifen chemoprevention trial, BMJ 330(7497) (2005) 932.

[112] C.L. Johnson, B.M. Rifkind, C.T. Sempos, M.D. Carroll, P.S. Bachorik, R.R. Briefel, D.J. Gordon, V.L. Burt, C.D. Brown, K. Lippel, et al., Declining serum total cholesterol levels among US adults. The National Health and Nutrition Examination Surveys, JAMA 269(23) (1993) 3002-8.

[113] N. Shin, Y.H. Kim, H. Xu, H.B. Shi, Q.Q. Zhang, J.P. Colon Pons, D. Kim, Y. Xu, F.Y. Wu, S. Han, B.B. Lee, L.S. Li, Redefining Budd-Chiari syndrome: A systematic review, World journal of hepatology 8(16) (2016) 691-702.

[114] L.D. DeLeve, D.C. Valla, G. Garcia-Tsao, D. American Association for the Study Liver, Vascular disorders of the liver, Hepatology 49(5) (2009) 1729-64.

[115] D. Valla, M.G. Le, T. Poynard, N. Zucman, B. Rueff, J.P. Benhamou, Risk of hepatic vein thrombosis in relation to recent use of oral contraceptives. A case-control study, Gastroenterology 90(4) (1986) 807-11.

[116] S. Lapner, N. Cohen, C. Kearon, Influence of sex on risk of bleeding in anticoagulated patients: a systematic review and meta-analysis, Journal of thrombosis and haemostasis : JTH 12(5) (2014) 595-605.

[117] W. Ren, X. Li, J. Jia, Y. Xia, F. Hu, Z. Xu, Prevalence of Budd-Chiari Syndrome during Pregnancy or Puerperium: A Systematic Review and Meta-Analysis, Gastroenterol Res Pract 2015 (2015) 839875.

[118] P.E. Rautou, A. Plessier, J. Bernuau, M.H. Denninger, R. Moucari, D. Valla, Pregnancy: a risk factor for Budd-Chiari syndrome?, Gut 58(4) (2009) 606-8.

[119] A. Aslan, A. Meyer Zu Vilsendorf, M. Kleine, M. Bredt, H. Bektas, Adult Kasabach-Merritt Syndrome due to Hepatic Giant Hemangioma, Case Rep Gastroenterol 3(3) (2009) 306-312.

[120] J.M. Perarnau, Y. Bacq, Hepatic vascular involvement related to pregnancy, oral contraceptives, and estrogen replacement therapy, Semin Liver Dis 28(3) (2008) 315-27.

[121] e.e.e. European Association for the Study of the Liver . Electronic address, EASL Clinical Practice Guidelines on the management of benign liver tumours, J Hepatol 65(2) (2016) 386-98.

[122] J. Guy, M.G. Peters, Liver disease in women: the influence of gender on epidemiology, natural history, and patient outcomes, Gastroenterol Hepatol (N Y) 9(10) (2013) 633-9.

[123] J.B. Rooks, H.W. Ory, K.G. Ishak, L.T. Strauss, J.R. Greenspan, A.P. Hill, C.W. Tyler, Jr., Epidemiology of hepatocellular adenoma. The role of oral contraceptive use, JAMA 242(7) (1979) 644-8.

[124] C.J. Bryant, R.J. Hoy, Oral contraceptive-induced hepatic adenoma and focal nodular hyperplasia, Australas Radiol 24(3) (1980) 289-92.

[125] T. Greer, Hepatic adenoma and oral contraceptive use, J Fam Pract 28(3) (1989) 322-6.

[126] K.R. Reddy, E.R. Schiff, Approach to a liver mass, Seminars in liver disease 13(4) (1993) 423-35.

[127] P. Aseni, C.V. Sansalone, C. Sammartino, F.D. Benedetto, G. Carrafiello, A. Giacomoni, C. Osio, M. Vertemati, D. Forti, Rapid disappearance of hepatic adenoma after contraceptive withdrawal, Journal of clinical gastroenterology 33(3) (2001) 234-6.

[128] K. Meissner, Hemorrhage caused by ruptured liver cell adenoma following long-term oral contraceptives: a case report, Hepato-gastroenterology 45(19) (1998) 224-5.

[129] H.A. Edmondson, T.B. Reynolds, B. Henderson, B. Benton, Regression of liver cell adenomas associated with oral contraceptives, Annals of internal medicine 86(2) (1977) 180-2.

[130] S. Rebouissou, P. Bioulac-Sage, J. Zucman-Rossi, Molecular pathogenesis of focal nodular hyperplasia and hepatocellular adenoma, J Hepatol 48(1) (2008) 163-70.

[131] J.C. Nault, P. Bioulac-Sage, J. Zucman-Rossi, Hepatocellular benign tumors-from molecular classification to personalized clinical care, Gastroenterology 144(5) (2013) 888-902.

[132] J. Ferlay, H.R. Shin, F. Bray, D. Forman, C. Mathers, D.M. Parkin, Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008, International journal of cancer 127(12) (2010) 2893-917.

[133] H. Feng, A.S. Cheng, D.P. Tsang, M.S. Li, M.Y. Go, Y.S. Cheung, G.J. Zhao, S.S. Ng, M.C. Lin, J. Yu, P.B. Lai, K.F. To, J.J. Sung, Cell cycle-related kinase is a direct androgen receptor-regulated gene that drives beta-catenin/T cell factor-dependent hepatocarcinogenesis, J Clin Invest 121(8) (2011) 3159-75.

[134] Z. Li, G. Tuteja, J. Schug, K.H. Kaestner, Foxa1 and Foxa2 are essential for sexual dimorphism in liver cancer, Cell 148(1-2) (2012) 72-83.

[135] W.L. Ma, C.L. Hsu, C.C. Yeh, M.H. Wu, C.K. Huang, L.B. Jeng, Y.C. Hung, T.Y. Lin, S. Yeh, C. Chang, Hepatic androgen receptor suppresses hepatocellular carcinoma metastasis through modulation of cell migration and anoikis, Hepatology 56(1) (2012) 176-85.

[136] M.W. Yu, C.J. Chen, Elevated serum testosterone levels and risk of hepatocellular carcinoma, Cancer Res 53(4) (1993) 790-4.

[137] J.M. Yuan, R.K. Ross, F.Z. Stanczyk, S. Govindarajan, Y.T. Gao, B.E. Henderson, M.C. Yu, A cohort study of serum testosterone and hepatocellular carcinoma in Shanghai, China, Int J Cancer 63(4) (1995) 491-3.

[138] K. Tanaka, H. Sakai, M. Hashizume, T. Hirohata, Serum testosterone:estradiol ratio and the development of hepatocellular carcinoma among male cirrhotic patients, Cancer Res 60(18) (2000) 5106-10.

[139] W.L. Ma, H.C. Lai, S. Yeh, X. Cai, C. Chang, Androgen receptor roles in hepatocellular carcinoma, fatty liver, cirrhosis and hepatitis, Endocr Relat Cancer 21(3) (2014) R165-82.

[140] D. Yang, D.L. Hanna, J. Usher, J. LoCoco, P. Chaudhari, H.J. Lenz, V.W. Setiawan, A. El-Khoueiry, Impact of sex on the survival of patients with hepatocellular carcinoma: a Surveillance, Epidemiology, and End Results analysis, Cancer 120(23) (2014) 3707-16.

[141] F. Farinati, A. Sergio, A. Giacomin, M.A. Di Nolfo, P. Del Poggio, L. Benvegnu, G. Rapaccini, M. Zoli, F. Borzio, E.G. Giannini, E. Caturelli, F. Trevisani, g. Italian Liver Cancer, Is female sex a significant favorable prognostic factor in hepatocellular carcinoma?, Eur J Gastroenterol Hepatol 21(10) (2009) 1212-8.

[142] W.M. Cong, M.C. Wu, X.H. Zhang, H. Chen, J.Y. Yuan, Primary hepatocellular carcinoma in women of mainland China. A clinicopathologic analysis of 104 patients, Cancer 71(10) (1993) 2941-5.

[143] P. Tangkijvanich, V. Mahachai, P. Suwangool, Y. Poovorawan, Gender difference in clinicopathologic features and survival of patients with hepatocellular carcinoma, World journal of gastroenterology 10(11) (2004) 1547-50.

[144] L. Benvegnu, A. Alberti, Patterns of hepatocellular carcinoma development in hepatitis B virus and hepatitis C virus related cirrhosis, Antiviral research 52(2) (2001) 199-207.

49

[145] C.M. Lam, J.L. Yong, A.O. Chan, K.K. Ng, R.T. Poon, C.L. Liu, C.M. Lo, S.T. Fan, Better survival in female patients with hepatocellular carcinoma: oral contraceptive pills related?, Journal of clinical gastroenterology 39(6) (2005) 533-9.

[146] R. Hefaiedh, R. Ennaifer, H. Romdhane, H. Ben Nejma, N. Arfa, N. Belhadj, L. Gharbi, T. Khalfallah, Gender difference in patients with hepatocellular carcinoma, Tunis Med 91(8-9) (2013) 505-8.

[147] I.O. Ng, M.M. Ng, E.C. Lai, S.T. Fan, Better survival in female patients with hepatocellular carcinoma. Possible causes from a pathologic approach, Cancer 75(1) (1995) 18-22.

[148] L. European Association For The Study Of The, R. European Organisation For, C. Treatment Of, EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma, J Hepatol 56(4) (2012) 908-43.

[149] P. Boudou-Rouquette, C. Narjoz, J.L. Golmard, A. Thomas-Schoemann, O. Mir, F. Taieb, J.-P. Durand, R. Coriat, A. Dauphin, M. Vidal, M. Tod, M.-A. Loriot, F. Goldwasser, B. Blanchet, Early Sorafenib-Induced Toxicity Is Associated with Drug Exposure and UGTIA9 Genetic Polymorphism in Patients with Solid Tumors: A Preliminary Study, PloS one 7(8) (2012) e42875.

[150] J. Ren, G.G. Chen, Y. Liu, X. Su, B. Hu, B.C. Leung, Y. Wang, R.L. Ho, S. Yang, G. Lu, C.G. Lee, P.B. Lai, Cytochrome P450 1A2 Metabolizes 17beta-Estradiol to Suppress Hepatocellular Carcinoma, PloS one 11(4) (2016) e0153863.

[151] C.C. Lee, G.Y. Chau, W.Y. Lui, S.H. Tsay, K.L. King, C.C. Loong, C.Y. Hshia, C.W. Wu, Better post-resectional survival in female cirrhotic patients with hepatocellular carcinoma, Hepatogastroenterology 47(32) (2000) 446-9.

[152] T. Poynard, P. Mathurin, C.L. Lai, D. Guyader, R. Poupon, M.H. Tainturier, R.P. Myers, M. Muntenau, V. Ratziu, M. Manns, A. Vogel, F. Capron, A. Chedid, P. Bedossa, P. Group, A comparison of fibrosis progression in chronic liver diseases, J Hepatol 38(3) (2003) 257-65.

[153] X. Wang, S.X. Lin, J. Tao, X.Q. Wei, Y.T. Liu, Y.M. Chen, B. Wu, Study of liver cirrhosis over ten consecutive years in Southern China, World J Gastroenterol 20(37) (2014) 13546-55.

[154] P.E. Chang, G.W. Wong, J.W. Li, H.F. Lui, W.C. Chow, C.K. Tan, Epidemiology and Clinical Evolution of Liver Cirrhosis in Singapore, Ann Acad Med Singapore 44(6) (2015) 218-25.

[155] A.A. Mokdad, A.D. Lopez, S. Shahraz, R. Lozano, A.H. Mokdad, J. Stanaway, C.J. Murray, M. Naghavi, Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis, BMC Med 12 (2014) 145.

[156] M. Blachier, H. Leleu, M. Peck-Radosavljevic, D.C. Valla, F. Roudot-Thoraval, The burden of liver disease in Europe: a review of available epidemiological data, J Hepatol 58(3) (2013) 593-608.

[157] W.R. Kim, R.S. Brown, Jr., N.A. Terrault, H. El-Serag, Burden of liver disease in the United States: summary of a workshop, Hepatology 36(1) (2002) 227-42.

[158] I. Simsek, G. Aslan, M. Akarsu, H. Koseoglu, A. Esen, Assessment of sexual functions in patients with chronic liver disease, Int J Impot Res 17(4) (2005) 343-5.

[159] M. Durazzo, A. Premoli, C. Di Bisceglie, S. Bo, E. Ghigo, C. Manieri, Male sexual disturbances in liver diseases: what do we know?, J Endocrinol Invest 33(7) (2010) 501-5.

[160] M. Sinclair, M. Grossmann, P.J. Gow, P.W. Angus, Testosterone in men with advanced liver disease: abnormalities and implications, J Gastroenterol Hepatol 30(2) (2015) 244-51.

[161] A. Karagiannis, F. Harsoulis, Gonadal dysfunction in systemic diseases, Eur J Endocrinol 152(4) (2005) 501-13.

[162] M. Grossmann, R. Hoermann, L. Gani, I. Chan, A. Cheung, P.J. Gow, A. Li, J.D. Zajac, P. Angus, Low testosterone levels as an independent predictor of mortality in men with chronic liver disease, Clin Endocrinol (Oxf) 77(2) (2012) 323-8.

[163] A.M. Allen, J.E. Hay, Review article: the management of cirrhosis in women, Aliment Pharmacol Ther 40(10) (2014) 1146-54.

[164] J. Tan, B. Surti, S. Saab, Pregnancy and cirrhosis, Liver Transpl 14(8) (2008) 1081-91.

[165] A.J. Montano-Loza, Clinical relevance of sarcopenia in patients with cirrhosis, World J Gastroenterol 20(25) (2014) 8061-71.

[166] T. Hanai, M. Shiraki, K. Nishimura, S. Ohnishi, K. Imai, A. Suetsugu, K. Takai, M. Shimizu, H. Moriwaki, Sarcopenia impairs prognosis of patients with liver cirrhosis, Nutrition 31(1) (2015) 193-9.

[167] B.A. Crawford, C. Kam, A.J. Donaghy, G.W. McCaughan, The heterogeneity of bone disease in cirrhosis: a multivariate analysis, Osteoporos Int 14(12) (2003) 987-94.

[168] J.D. Collier, M. Ninkovic, J.E. Compston, Guidelines on the management of osteoporosis associated with chronic liver disease, Gut 50 Suppl 1 (2002) i1-9.

[169] S.M. Kawut, M.J. Krowka, J.F. Trotter, K.E. Roberts, R.L. Benza, D.B. Badesch, D.B. Taichman, E.M. Horn, S. Zacks, N. Kaplowitz, R.S. Brown, Jr., M.B. Fallon, G. Pulmonary Vascular Complications of Liver Disease Study, Clinical risk factors for portopulmonary hypertension, Hepatology 48(1) (2008) 196-203.

[170] G. Castano, S. Sookoian, Female sex and autoimmune hepatitis and the risk of portopulmonary hypertension, Hepatology 48(6) (2008) 2090.

[171] M.J. Silva, M.V. Rosa, P.J. Nogueira, F. Calinas, Ten years of hospital admissions for liver cirrhosis in Portugal, Eur J Gastroenterol Hepatol 27(11) (2015) 1320-6.

[172] V. Giannelli, M. Giusto, A. Farcomeni, F.R. Ponziani, M. Pompili, R. Vigano, R.M. Iemmolo, M.F. Donato, M. Rendina, P. Toniutto, L. Pasulo, M.C. Morelli, E. De Martin, L. Miglioresi, D. Di Paolo, S. Fagiuoli, M. Merli, A.R.-C.g. study, Treatment of hepatitis C recurrence is less successful in female than in male liver transplant recipients, Transpl Int 25(4) (2012) 448-54.

[173] K. Waki, UNOS Liver Registry: ten year survivals, Clin Transpl (2006) 29-39.

[174] A.K. Mathur, D.E. Schaubel, Q. Gong, M.K. Guidinger, R.M. Merion, Sex-based disparities in liver transplant rates in the United States, Am J Transplant 11(7) (2011) 1435-43.

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