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Review

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.

Contents

1. 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

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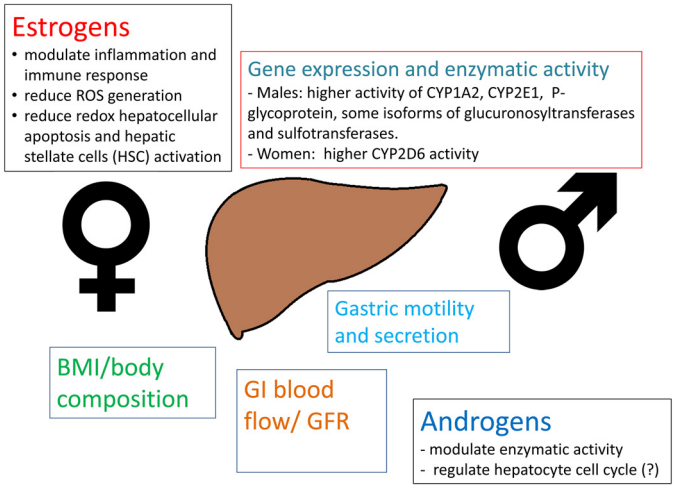

Fig. 1. Major determinants of gender-based differences in liver toxicity and damage. *Abbreviations*: ROS, reactive oxygen species; BMI, body mass index; GI, gastrointestinal; GFR, glomerular filtration rate; CYP, cytochrome P450 isoenzyme.

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.

2. 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.

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] (Fig. 1).

Gender-specific differences in gene expression or activity of drug metabolising 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].

3. Liver disease from toxic cause

3.1. 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].

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].