Sex Differences in Drug-Induced Liver Injury: 💊 Same Pills, Different Thrills? 💊

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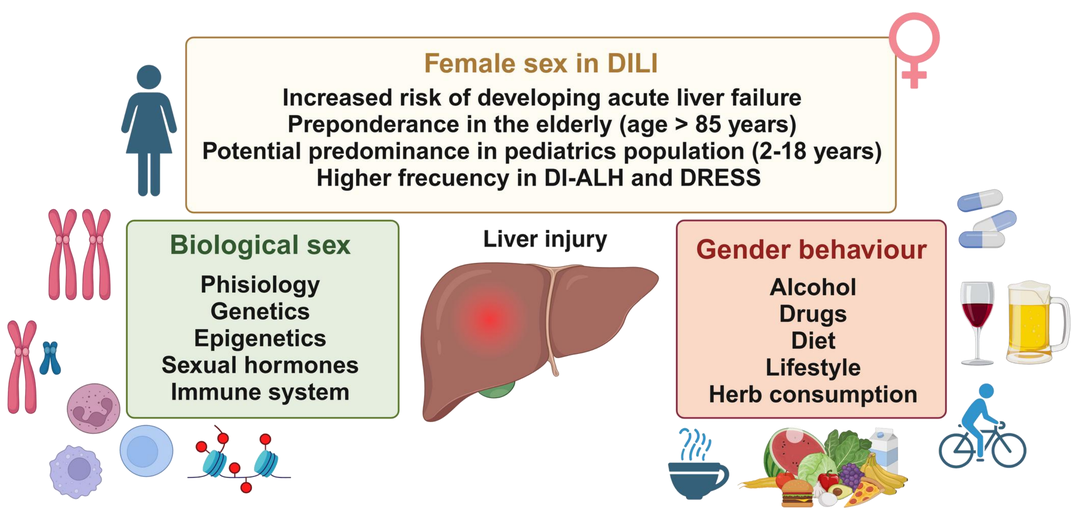

Figure 1. Biological, gender and specific-female factors that contributes to drug-induced liver injury development and/or progression.

INTRODUCTION

Idiosyncratic drug-induced liver injury (DILI) is an unpredictable and host-dependent adverse reaction due to the use of drugs and herbal and dietary supplements (HDS) that poses a significant challenge in clinical practice and public health. DILI is considered a complex and multilayered condition, in which reactive metabolite production, oxidative stress, mitochondrial dysfunction, and immune-mediated hepatotoxicity play an essential role. Drug properties, environmental and host factors (including biological sex and gender behaviour differences), can also have a major impact. Particularly, biological female sex presents specific clinical features that potentially contribute to dimorphism in DILI **(Figure 1)**.

DISCUSSION

Clinical registries in DILI are efficient tools for expanding knowledge about this multilayered disease, identifying at-risk populations, and promoting the implementation of personalized safety medicine. Female sex is overrepresented in different registries around the world **(Figure 2)**, specially in the senior and pediatric population groups. These differences might arise from sex and gender-specific drug usage as occurs with hormonal therapy, HDS, nitrofurantoin, and others. In fact, some DILI causative agents, seem to be strongly related to female sex **(Figure 3)**.

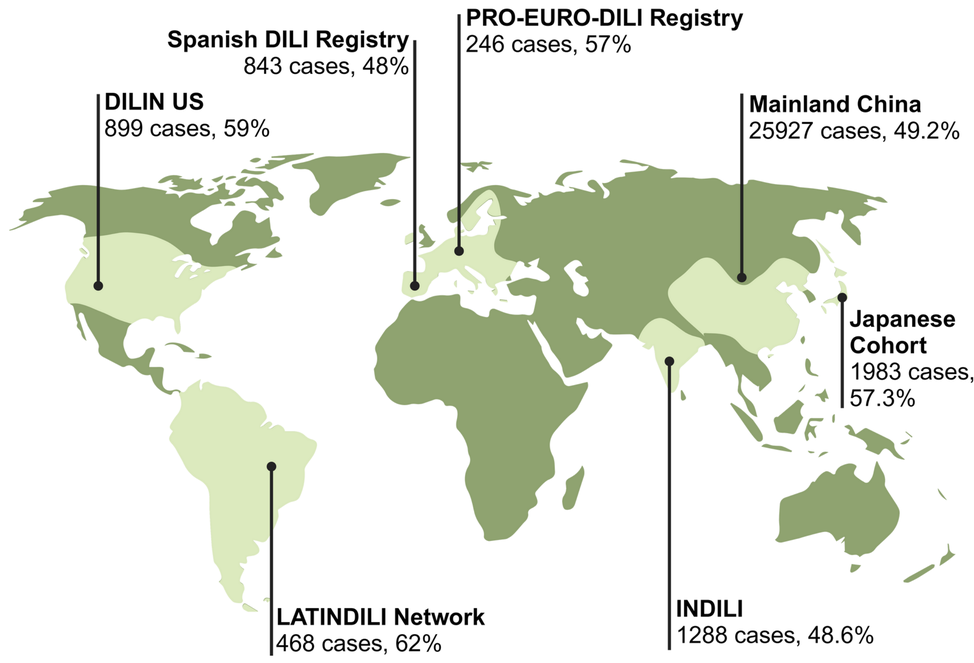

Figure 2. Female sex frequency in drug Induced liver injury registries and cohorts across the world.

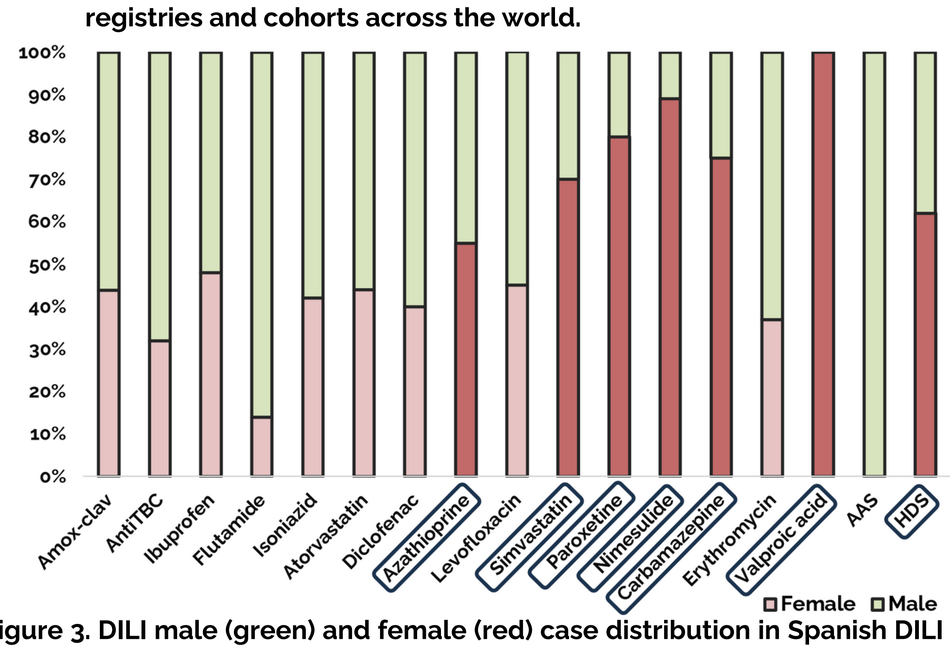

Figure 3. DILI male (green) and female (red) case distribution in Spanish DILI Registry along with culprit drugs. HDS: Herbal and dietary supplements; amox-clav (amoxicillin-clavulanate); antiTBC (antituberculosis drugs); AAS (anabolic androgenic steroids). In dark red, female prevalence higher than 50%.

The higher risk of ADRs and worse outcomes observed in females compared to males may be attributed to sexual dimorphism in diverse biological mechanisms (**Figure 4**). Sex hormones influence the expression of key genes involved in phases I and II of drug metabolism within hepatocytes. This, together with a higher body fat percentage—which affects plasma levels of lipophilic drugs—and lower blood albumin levels may also contribute to pharmacokinetic differences in DILI influenced by sex. Furthermore, immune-mediated mechanisms are also influenced by sex hormones. Females have more robust innate and adaptive immune responses than males, which predisposes them to immune-mediated or inflammatory diseases, strongly related to DILI. Epigenetics may also influence sex-specific differences in DILI; some immune-related genes may escape X-chromosome inactivation, potentially influencing immune responses and susceptibility to DILI.

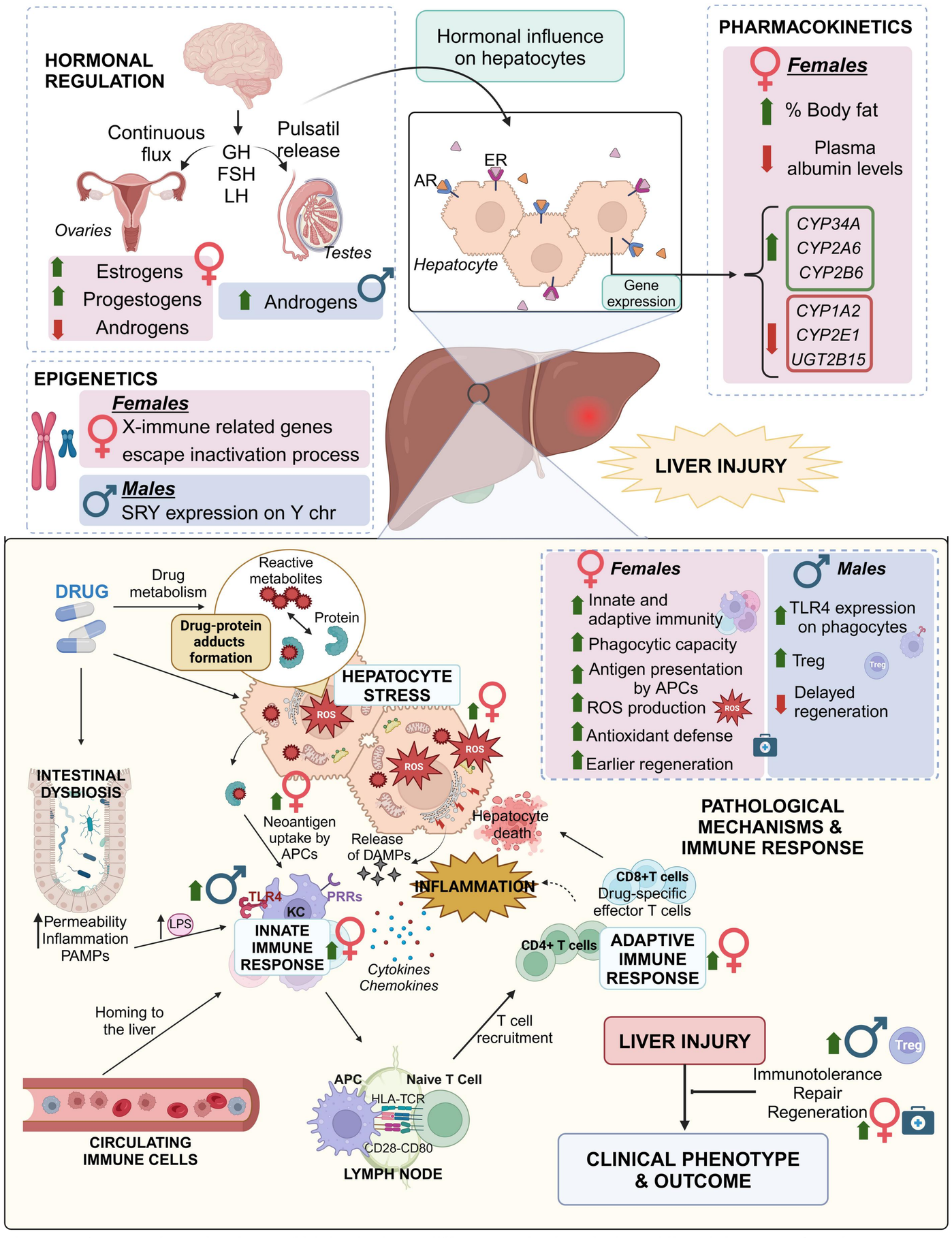

Figure 4. Proposed mechanisms of biological sex differences in drug induced liver injury onset and progression.

<u>TAKE HOME MESSAGE:</u> Female-specific features influence DILI development and progression. A better understanding of these sex differences will contribute to improved **clinical management of female DILI patients, leading to personalised precision medicine.**

References in: