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Drug-induced liver injury in obesity

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Many countries are facing an epidemic of obesity that can be explained, at least in part, by a sedentary life style and calorie overconsumption. This poses a major issue for public health since obesity primarily enhances the risk of various illnesses such as type 2 diabetes, coronary heart disease, some cancers and non-alcoholic fatty liver disease (NAFLD). Consequently, obese patients are consuming on average more drugs than non-obese individuals [1]. This could pose another medical issue, in particular for hepatologists, since many drugs are able to induce liver injury [2,3]. Moreover, there is growing evidence that obesity and NAFLD can increase the risk of drug-induced liver injury (DILI), at least for some drugs [3,4]. Thus, obese patients could be more prone to develop DILI as a consequence of drug overconsumption and an intrinsic susceptibility of their diseased liver to drug-induced hepatotoxicity.

Actually, DILI in obese patients could occur as two distinct clinical settings. Indeed, in the context of obesity and related metabolic diseases, some drugs seem to aggravate pre-existing NAFLD whereas others could induce more frequently an acute hepatitis (Fig. 1). Drugs that could aggravate NAFLD in obese patients are tamoxifen, irinotecan, methotrexate and nucleoside reverse transcriptase inhibitors (NRTIs) such as stavudine and didanosine (Table 1 in Fig. 1) [3,5–7]. Aggravation of NAFLD has also been documented in different animal models with rosiglitazone, tetracycline, phenobarbital and pentoxifylline (Table 1 in Fig. 1) [3,8]. Drugs that could induce acute liver injury more often in obese individuals are the volatile halogenated anesthetic halothane and isoflurane, acetaminophen (APAP), and other drugs such as losartan, ticlopidine and omeprazole (Table 1 in Fig. 1) [3,9–11]. However, it is noteworthy that the list of drugs in Table 1 is temporary and should expand in the future as DILI in the context of obesity is gaining growing attention. In this "*Snapshot*" article, I will put forward several potential mechanisms whereby drugs can be more hepatotoxic in obese individuals. Since these mechanisms have mostly been discovered during experimental studies, any extrapolation to humans should be done with caution.

Drug-induced worsening of NAFLD could be explained by different mechanisms (Fig. 1B). Regarding fatty liver, some drugs could be able to stimulate lipogenesis in steatotic liver, but not in normal liver, by activating lipogenic transcription factors such as peroxisome proliferator-activated receptor-γ (PPARγ) (e.g. rosiglitazone), pregnane X receptor (e.g. tamoxifen) and carbohydrate response element-binding protein (e.g. pentoxifylline) [3,8]. Because numerous drugs are able to alter mitochondrial function [2,3], it is conceivable that impaired mitochondrial fatty acid oxidation (mtFAO) could also be involved in drug-induced aggravation of fatty liver. Importantly, increased FAO during NAFLD is a key adaptive mechanism in order to restrain fat accretion [12,13], and thus any impediment to this adaptation could significantly aggravate fatty liver (Fig. 1B). Reduced VLDL secretion could be involved, as several drugs were shown to interfere with VLDL synthesis by inhibiting microsomal triglyceride transfer protein (MTP) activity (e.g. amiodarone, tianeptine) [14] or apolipoprotein B-100 synthesis (e.g. mipomersen) [15] (Fig. 1B). Some drugs are also able to induce oxidative stress [3,16], which can trigger the progression of simple steatosis to non-alcoholic steatohepatitis (NASH) (Fig. 1B). Drug-induced oxidative stress could have several origins, in particular through glutathione (GSH) depletion and inhibition of the mitochondrial respiratory chain (MRC) [3,16]. The pre-existent reduction of GSH levels and MRC activity in NAFLD [12] could prime drug-induced oxidative stress and accelerate the progression of fatty liver to NASH. Unlike ethanol overconsumption, which is known to aggravate NAFLD [4,17], it is still unknown whether drugs able to aggravate NAFLD can stimulate the production of proinflammatory and fibrogenic cytokines such as TNFα and TGFβ, respectively.

It is worth mentioning that drug-induced aggravation of NAFLD can also be secondary to the worsening of insulin resistance (IR), a key mechanism leading to hepatic lipid deposition (Fig. 1A). Indeed, worsening of IR exacerbates not only hepatic lipogenesis secondary to hyperinsulinemia but also the delivery of free fatty acids (FFA) to the liver due to adipose triacylglycerol hydrolysis. Drugs known to trigger (or worsen) IR are, for instance, synthetic corticosteroids, antipsychotic drugs (e.g. clozapine, olanzapine), NRTIs, protease inhibitors and thiazide diuretics (e.g. hydrochlorothiazide) [3,5–7,18].

Higher risk of drug-induced acute hepatitis in obesity could be related to increased activity of several cytochromes P450 (CYPs), which could enhance the generation of toxic metabolites (Fig. 1C). Indeed, increased activity of several CYPs such as CYP1A2, CYP2C9, CYP2D6 and CYP2E1 has been documented in obese individuals [4,19]. Higher CYP2E1 activity could explain why drugs such as halothane and APAP seem to be more hepatotoxic in the context of obesity and NAFLD since CYP2E1 transforms these drugs into the highly reactive metabolites trichloroacetyl chloride and N-acetyl-*p*-benzoquinone imine

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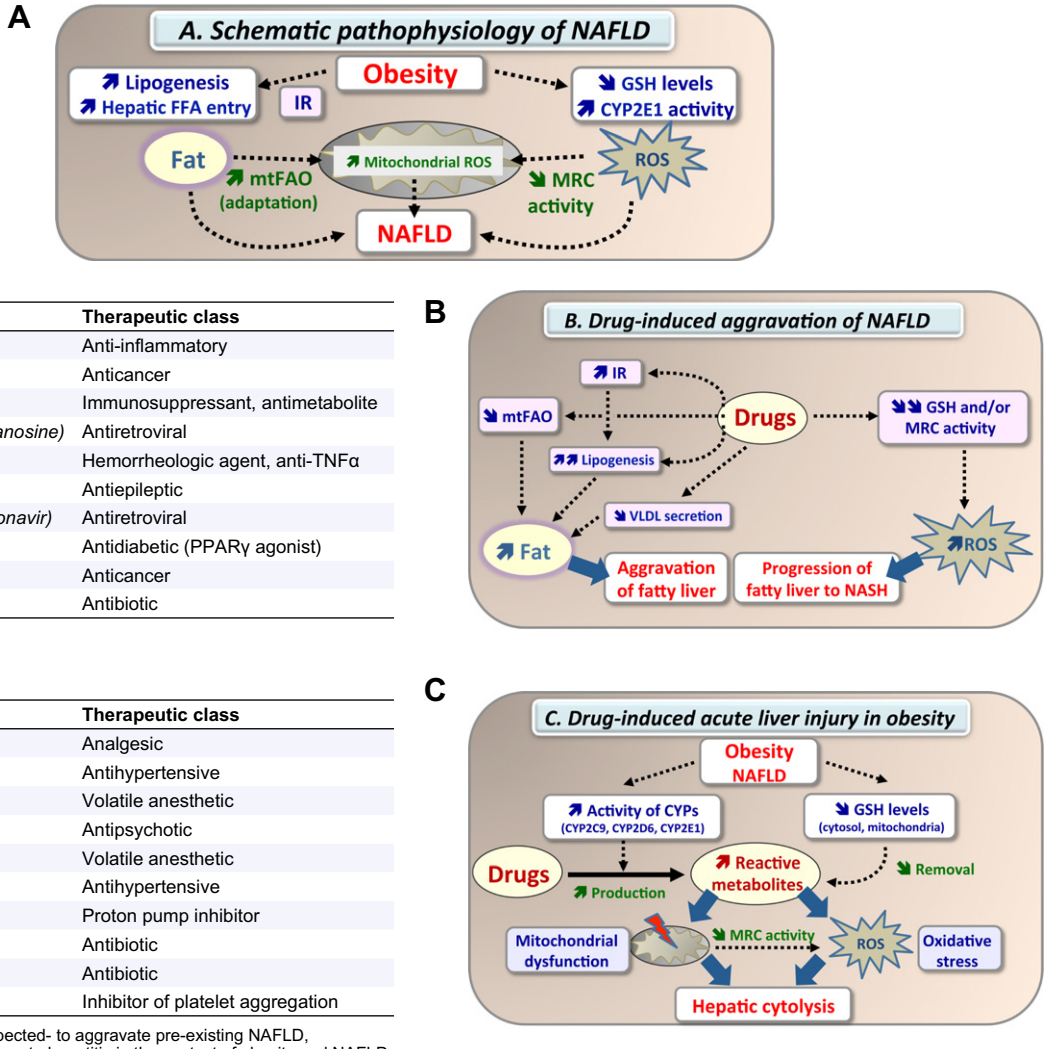
Hepatology Snapshot



Aggravation of pre-existing NAFLD

Drugs	Therapeutic class
Corticosteroids	Anti-inflammatory
Irinotecan	Anticancer
Methotrexate	Immunosuppressant, antimetabolite
NRTIs (e.g., stavudine, didanosine)	Antiretroviral
Pentoxifylline	Hemorrheologic agent, anti-TNFα
Phenobarbital	Antiepileptic
Protease inhibitors (e.g., ritonavir)	Antiretroviral
Rosiglitazone	Antidiabetic (PPARγ agonist)
Tamoxifen	Anticancer
Tetracycline	Antibiotic

Acute hepatitis in obesity and NAFLD

Drugs	Therapeutic class
Acetaminophen (APAP)	Analgesic
Fosinopril	Antihypertensive
Halothane	Volatile anesthetic
Haloperidol	Antipsychotic
Isoflurane	Volatile anesthetic
Losartan	Antihypertensive
Omeprazole	Proton pump inhibitor
Piperacillin-Tazobactam	Antibiotic
Telithromycin	Antibiotic
Ticlopidin	Inhibitor of platelet aggregation

Table 1. Drugs shown - or suspected- to aggravate pre-existing NAFLD, or to induce more frequently an acute hepatitis in the context of obesity and NAFLD, according to clinical (in italics) and experimental investigations

Fig. 1. Schematic pathophysiology of obesity-associated non-alcoholic fatty liver disease (NAFLD) and mechanisms whereby some drugs can induce, or aggravate, liver injury in the context of NAFLD.

(NAPQI), respectively [4,20]. When generated in excess, these reactive metabolites can induce hepatic oxidative stress, severe mitochondrial dysfunction and cytolysis (Fig. 1C) [4,20]. It is noteworthy that higher risk of APAP-induced acute liver injury in obese individuals with NAFLD is mostly suspected in the context of APAP overdose [10,21], although therapeutic doses of this pain killer could also be involved [22]. Another mechanism that could explain higher risk of drug-induced acute hepatitis in obesity is reduced levels of GSH, in particular at the mitochondrial level [12], which could impair the removal of CYP-generated reactive metabolites (Fig. 1C). Because obesity is associated with reduced activity of some CYPs such as CYP3A4 [19], higher risk of acute hepatitis is not expected with all drugs able to generate toxic metabolites. Moreover, enhanced glucuronosyltransferase activity seems to be common in obesity [19,20], which may favor the detoxication of some compounds. Finally, it is also noteworthy that under-dosing is expected with drugs whose dosage is not adapted to higher body mass index. Clearly, more investigations are needed in order to decipher the mechanisms whereby some drugs are more toxic on the obese liver. From a clinical viewpoint, a better identification of the drugs presenting such harmful effects is urgently warranted. This should prompt physicians to carry out a regular monitoring of liver function in obese patients treated with these drugs in order to detect any deterioration of the pre-existing NAFLD, or the occurrence of acute hepatitis.

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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