

Results: Fifty-two patients (94 % female, 57 ± 11 years, BMI 25 ± 6 kg m⁻², histological stages 1(n23)/2(n16/3(n13) completed follow-up. ALP normalised in 36 % with UDCA, 78 % with UDCA+BZF 400 mg and 100 % with UDCA+BZF 800 mg ($\chi^2 < 0.01$). Mean ALP ($\times$ ULN) at six months was 1.5 ± 0.7 (UDCA), 0.98 ± 0.2 (UDCA+BZF 400 mg), and 0.8 ± 0.2 (UDCA+BZF 800 mg) (ANOVA $p < 0.001$). Linear mixed-effects analysis showed significant time-dependent ALP declines in all groups; BZF intensified these monthly slopes ($\beta = -0.34$ for 400 mg, -0.44 for 800 mg vs UDCA, both Tukey-adjusted $p < 0.01$). Pruritus persisted in 14 % of UDCA recipients but in none on BZF, and renal function and creatine kinase were unchanged across groups.

Conclusions: Up-front UDCA+BZF achieves dose-dependent, near-universal six-month ALP normalisation and accelerates biochemical improvement without early safety concerns. These interim data support initiating combination therapy at diagnosis, particularly in symptomatic PBC.

Conflict of interest: None

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STEATOTIC HEPATOCYTES SHOWN REDUCED CYP450 EXPRESSION AND IN VITRO RESISTANCE TO DRUG-INDUCED TOXICITY

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Introduction and Objectives: Metabolic dysfunction-associated steatotic liver disease (MASLD), has been associated with dysregulation of CYP450 enzymes, resulting in an altered drug-metabolizing profile. It has been suggested that lipid droplets (LDs) might influence CYP450 expression and function. Diclofenac (DF) and acetaminophen (APAP) are common analgesics that can cause drug-induced liver injury (DILI), due to their toxic metabolites produced by CYP450 dependent reactions. The aim of this study was to characterize the effect of lipid droplets present in hepatocytes on drug-induced toxicity.

Materials and Methods: Steatotic Zucker rat hepatocytes (Fa/Fa) (chronic lipid accumulation) or free fatty acid (FFA)-treated Wistar rat hepatocytes (acute lipid accumulation) were treated with DF (400 μ mol/L) or APAP (20 mmol/L). Caspase-3 activity, necrotic cell death and mitochondrial ROS production were determined. mRNA levels of different CYP450 related with diclofenac and APAP metabolism, were quantified by RT-qPCR. Lipid droplets quantity and distribution were assessed by BODIPY staining. To compare our results with the human data available we performed in silico analysis using transcriptomic databases from patients with hepatic steatosis.

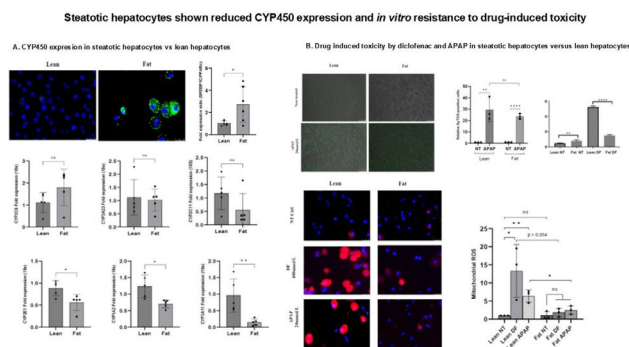
Results: Decreased expression of CYP2E1 and CYP3A11(CYP3A4 human homologue) was observed in steatotic Zucker rat hepatocytes. No regulation of CYP450 expression was observed in FFA-treated Wistar hepatocytes (acute lipid accumulation). Lipid droplets

reduced mitochondrial ROS production and prevented apoptotic and necrotic cell death induced by DF and APAP, respectively. Changes in lipid droplet distribution were also observed in DF and APAP treated hepatocytes. In Silico analysis using transcriptomic human data available are now in progress to compare these findings and their relevance in the context of MASLD.

Conclusions: Lipid droplets are associated with protective mechanisms during drug-induced toxicity due to the downregulation of CYP450 gene expression and prevention of ROS production. Further studies are needed to understand the exact mechanisms and molecular targets regulated by LDs that influence drug-induced toxicity.

Conflict of interest: None

Graphical Abstract_Steatotic hepatocytes shown reduced CYP450 expression and in vitro resistance to drug-induced toxicity



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PROJECTED CLINICAL AND ECONOMIC BURDEN OF METABOLIC DYSFUNCTION–ASSOCIATED STEATOHEPATITIS IN BRAZIL: A 20-YEAR FORECAST ACROSS TYPE 2 DIABETES STATUS

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Introduction and Objectives: Type 2 diabetes (T2D) is an important risk factor for metabolic dysfunction–associated steatohepatitis (MASH) and its complications.

Explore long-term impact economic burden of MASH among adults by T2D status.

Patients and Methods: Markov model simulated the natural history of patients with MASH in Brazil over a 20-year horizon (2021–2040).