Intracellular lipids: an independent cause of liver injury and chronic kidney disease in non-alcoholic fatty liver disease-like context

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Introduction: Ectopic lipid accumulation in the liver and kidneys is a hallmark of metabolic diseases, such as obesity and diabetes, leading to non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD). Interestingly, ectopic lipid accumulation in both the liver and kidneys is also an important feature of a rare metabolic disease named Glycogen Storage Disease type Ia (GSDIa). GSDIa is caused by glucose-6 phosphatase catalytic subunit (G6PC) deficiency, entailing hypoglycaemia during short fasts. Moreover, G6Pase deficiency leads to glucose-6 phosphate accumulation in the liver and kidneys, leading to glycogen and lipid accumulation. With time, this results in the development of the same hepatic and renal long-term complications as obesity and diabetes, meaning NAFLD and CKD. Finally, in the obesity/diabetes field recent data have highlighted a strong correlation between NAFLD and CKD incidences. In this study, we first investigated whether and how a diet enriched in lipids could accelerate liver or kidney injuries in two mouse model of GSDIa with a specific deletion of *G6pc* in the liver or kidneys (L.G6pc$^{-/-}$ and K.G6pc$^{-/-}$ respectively). In parallel, using the same mouse models, we examined whether a drug activating intracellular lipid catabolism could prevent or delay NAFLD and CKD, respectively. Finally, a part of this study also allowed us to document whether NAFLD can influence the development of CKD or not.

Method: L.G6pc$^{-/-}$ and K.G6pc$^{-/-}$ mice were fed either a high fat high sucrose (HF/HS) or a standard (STD) diet for 9 months. A group of mice was fed a STD diet for 6 months and then with a fenofibrate-enriched diet for 3 additional months. After 9 months, lipid and glycogen metabolism were characterized, and NAFLD and CKD damages were evaluated.

Results: HF/HS diet exacerbated hepatic and renal lipid accumulation in L.G6pc$^{-/-}$ and K.G6pc$^{-/-}$ mice respectively. In L.G6pc$^{-/-}$ mice, this resulted in an increase in liver injuries, characterized by higher levels of plasmatic transaminase, and increased hepatic tumor incidence. In K.G6pc$^{-/-}$ mice, HF/HS diet accelerated the nephropathy, illustrated by an increase of urinary albumin and lipocalin 2 levels, and advanced fibrosis. In both cases the worsening of NAFLD injuries and CKD was independent of glycogen content. Furthermore, fenofibrate, *via* the activation of lipid oxidation, significantly decreased the hepatic or renal lipid accumulations and prevented liver or kidney damages in L.G6pc$^{-/-}$ and K.G6pc$^{-/-}$ mice. Finally, we show that L.G6pc$^{-/-}$ and K.G6pc$^{-/-}$ mice developed NAFLD and CKD independently.

Conclusion: This study highlights the crucial role that lipids play in the independent development of both NAFLD and CKD and demonstrates the importance of lipid-lowering treatments in various metabolic diseases featured by lipid load, from the "rare" GSDIa to the "epidemic" morbid obesity or type 2 diabetes.