Human Hepatocytes in Experimental Steatosis: Influence of Donor Sex and Sex Hormones

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Abstract

Background/Objectives: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a sexually dimorphic condition, with higher prevalence in men than in women. Sex differences in hepatic lipid metabolism and the modulatory role of sex hormones have been described but are still insufficiently understood. The aim of this study was to introduce the variables sex and sex hormones into a human in vitro model of hepatic steatosis. Methods: Primary human hepatocytes (PHHs) were isolated from male and female donors, treated with free fatty acids (FFA) to induce steatosis, and further exposed to physiological concentrations of estrogen, progesterone, or testosterone. Intracellular triacylglyceride (TAG) content, lipid droplet (LD) formation, FFA uptake, and very-low-density lipoprotein (VLDL) excretion were assessed. In parallel, the expression of lipid metabolism-related genes was quantified by qPCR. Results: FFA treatment induced comparable uptake and intracellular TAG storage in both sexes. However, female PHHs secreted approximately twice as many VLDL particles as male cells. Steatosis significantly increased expression of LDLR, CPT2, and PLA1A only in male PHHs. Sex hormones exerted distinct, sex-specific effects: estrogen reduced TAG accumulation in female PHHs; whereas testosterone reduced TAG in male but increased it in female PHHs after prolonged treatment. LD characterization confirmed sex- and hormone-dependent differences in lipid storage patterns. In male PHHs, progesterone promoted lipid storage and increased apoB-100 secretion, accompanied by reduced LDLR and APOA5 expression, and testosterone increased the FFA-mediated CPT2 even further. Conclusions: Sex and sex hormones distinctly shape hepatocellular lipid handling under steatotic conditions. While female PHHs demonstrated greater lipid excretion capacity, male PHHs exhibited stronger transcriptional responses. Sex-specific responses to estrogen and testosterone resembled clinical observations on sex hormone effects. These findings highlight the need to account for sex-specific differences in MASLD pathophysiology and therapeutic strategies.