

# The importance of the long-chain polyunsaturated fatty acid n-6/n-3 ratio in development of non-alcoholic fatty liver associated with obesity

Valenzuela, Rodrigo

Videla, Luis A.

Non-alcoholic fatty liver disease (NAFLD) is the most important cause of chronic liver disease that is characterized by hepatocyte triacylglycerol accumulation (steatosis), which can progress to inflammation, fibrosis, and cirrhosis (steatohepatitis). Overnutrition triggers the onset of oxidative stress in the liver due to higher availability and oxidation of fatty acids (FA), with development of hyperinsulinemia and insulin resistance (IR), and n-3 long-chain polyunsaturated FA (n-3 LCPUFA) depletion, with enhancement in the n-6/n-3 LCPUFA ratio favouring a pro-inflammatory state. These changes may lead to hepatic steatosis by different mechanisms, namely, (i) IR-dependent higher peripheral lipolysis and FA flux to the liver, (ii) n-3 LCPUFA depletion-induced changes in DNA binding activity of sterol regulatory element-binding protein 1c (SREBP-1c) and peroxisome proliferator-activated receptor  $\alpha$  (PPAR- $\alpha$ ) favouring lipogenesis over FA oxidation, and (iii) hyperinsulinemia-induced acti