

## PHARMACOLOGICAL MODULATION OF METABOLIC, HORMONAL, AND INFLAMMATORY ALTERATIONS IN AN EXPERIMENTAL MODEL OF HEPATIC STEATOSIS

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**Introduction:** Nonalcoholic fatty liver disease (NAFLD) is considered as a common cause of chronic liver disease in children. This condition is frequently associated with other metabolic disorders, such as obesity, diabetes and hyperlipidemia. The aim of this research is the study of several pharmacological treatments in an experimental model of NAFLD in order to clarify the pathogenetic mechanisms involved in its onset, and evaluate pharmacological therapies.

**Methods:** Hepatic steatosis was induced in young male Sprague Dawley rats (113±2.5g, 7 weeks-old), fed for 4 weeks with High-Fat Lieber-DeCarli diet (HFD), or control diet (CD). Groups of HFD rats (n=6) were treated orally with antioxidant (vitamin E, 250mg/kg/die), or probiotic (VSL#3, high-concentration probiotic preparation of *Lactobacillus casei*, *L. plantarum*, *L. acidophilus*, and *L. delbrueckii* subsp. *Bulgaricus* plus *Bifidobacterium longum*, *B. breve*, and *B. infantis*, and *Streptococcus salivarius* subsp. *Thermophilus*, 13x10<sup>9</sup>/kg/die) or antidiabetic (metformin, 250mg/kg/die) drugs. During the experimental time, food intake and weight gain were registered, and body fat content analyzed through a bioelectrical impedance analyzer. At the end of the experimental time, rats were sacrificed, blood (for metabolic parameters and leptin level determination) collected and liver excised for the evaluation of TBARS content, 3-nitrotyrosine and PPAR- $\alpha$  expression by Western blot analysis.

**Results:** No significant difference in body weight and food intake was evidenced between HFD and CD groups, while a slight increase in body fat content was observed in HFD animals, which well correlated with increased leptinemia. Livers from HFD rats showed a significant increase both in the presence of nitrotyrosine on hepatic proteins, a marker for peroxynitrite formation, and in free TBARS level, a marker of lipid peroxidation. All drug treatments ameliorated hepatic nitrosylation, among these vitamin E and VSL#3 treatments significantly decreased lipid peroxidation levels. VSL#3 and metformin treatments reduced body weight, fat mass and leptin levels in HFD animals (p<0.05). Serum parameters determination evidenced that glycemia, cholesterol, AST and ALT were similar in all groups, only triglycerides levels were found to be elevated in the HFD rats and VSL#3 treatment significantly reduced this parameters. After 4 weeks of diet, PPAR  $\alpha$  protein expression was significantly attenuated in the HFD group vs CD and VSL#3 and vitamin E treatments restored PPAR- $\alpha$  levels.

**Conclusion:** We documented that vitamin E, VSL#3 and metformin improved fatty liver disease, identifying a potential treatment for NAFLD in humans.