

Mitigation of High-Fat Diet-Induced Liver Injury in MS-NASH Mice: Modifications in Proteomic Signature

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming the most important cause of liver damage in Western society. Non-alcoholic steatohepatitis (NASH) represents an advanced stage of NAFLD. Our previous long-term murine studies have shown the beneficial role of a red marine algae-derived multi-mineral (calcium, magnesium, multiple trace element-rich) supplement (Aquamin) in reducing liver injury and decreasing liver tumor incidence. The purpose of the present study was to determine how manifestations and effects of NASH can be mitigated by use of Aquamin. ***Methods:*** Two cohorts of MS-NASH mice were placed on a high-fat Western diet (HFWD) with and without mineral supplementation for a period of 16 weeks. A group of mice (C57BL/6) on regular chow was included as a control. During the in-life phase of the study, weight changes were assessed weekly. At the time of euthanasia, livers were assessed histologically for steatosis and fibrosis by using Sirius red staining. Liver tissue samples were also evaluated using a tandem mass tag (TMT) mass-spectroscopic proteomic approach for protein expression levels in individual animals. ***Results:*** Mice on the HFWD gained more weight than animals on the control diet. However, there was no overall change in weight for mice fed a high-fat diet, irrespective of mineral intervention. On histological assessment, there was no difference in the steatosis between two high-fat groups but mice on Aquamin have shown reduced Sirius red staining or collagen deposition as compared to placebo mice. Regarding proteomic profile, there was a clear distinction among control and high-fat groups. Placebo (high-fat diet alone) mice were used for comparison. Mice fed a high-fat diet with Aquamin intervention upregulated 39 unique pathways with a p-value less than 0.05 as assessed by the Reactome database. Pathways significantly impacted by Aquamin intervention include but are not limited to the following: formation of cornified envelope; keratinization; gap junction assembly; type I hemidesmosome assembly; apoptosis-related pathways; plasma lipoprotein assembly, remodeling, and clearance; and hedgehog 'off' state pathways. ***Conclusion:*** An addition of certain dietary minerals may have a protective role in interfering downstream advancement from steatosis to NASH, a serious manifestation of liver injury. This preliminary work warrants additional studies to pursue the role of these minerals in the context of high-fat diet-induced liver injury.