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INCREASED OXIDATIVE CAPACITY OF CIRCULATING POLYMORPHONUCLEAR NEUTROPHILS (PMNS) IN NON-DIABETIC NASH PATIENTS

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Background: Inflammation and oxidative stress are key factors in the pathogenesis of non-alcoholic steatohepatitis (NASH). Polymorphonuclear neutrophils are capable to produce significant amounts of reactive oxygen species (ROS) via the NADPH oxidase complex. Increased hepatic neutrophil infiltration has been described in steatohepatitis. We aimed to investigate the in vitro ROS generation by neutrophils of NASH patients and the hepatic NADPH oxidase activity in murine steatohepatitis.

Material and methods: PMNs were isolated from peripheral blood of NASH patients (n=16) and healthy controls (n=16). In vitro ROS production was measured by luminol chemiluminescence after phorbol myristate acetate (PMA) or opsonized zymosan stimulation. Hepatic lipid peroxidation and NADPH oxidase activation were measured in mice fed with methionine-choline-deficient (MCD) or -supplemented (MCS) diets.

Results: PMA activated oxidative burst both in patients and controls. However, ROS production was significantly increased in non-diabetic NASH patients (n=9) compared to controls 30 min after the PMA stimulation. PMNs from NASH patients with diabetes mellitus (n=7) did not have higher ROS production after PMA-stimulation compared to controls. The PMA-induced peak chemiluminescence was significantly higher in the non-diabetic NASH patients compared to controls and diabetic NASH patients. No significant difference was observed without any stimulation and in opsonized zymosan induced chemiluminescence. Consistent with the increased oxidative capacity of PMNs in NASH patients, we found increased hepatic lipid peroxidation, higher expression and activation of the NADPH oxidase complex in MCD-steatohepatitis.

Conclusion: Our finding supports the role of neutrophil oxidative stress in NASH. Our novel data suggests that the increased oxidative capacity of the PMNs it is not only localized to the liver but can have systemic effects and serve as a potential biomarker of NASH.