

In vivo MRS analysis of Non-Alcoholic Fatty Liver Disease in a translational model for the metabolic syndrome

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Introduction

The metabolic syndrome is characterized by the co-occurrence of several risk factors, such as obesity, insulin resistance, dyslipidemia, and inflammation which eventually may lead to the development of complications in various organs. Prominent pathology herein is the currently untreatable liver cirrhosis, which is preceded by non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis. Ideally, diseased liver status should be detected as early as possible. Since histopathological evaluation of liver biopsies are clinically not-feasible, non-invasive Magnetic Resonance Spectroscopy (MRS) is used to assess liver fat content as a surrogate marker for liver pathology.

Aim

Adaptation of a clinically used non-invasive quantification method to assess NAFLD in a relevant preclinical model for the metabolic syndrome.

Methods

APOE*3Leiden.CETP mice (n=4-5 per group) were fed a High Fat Diet (HFD) containing 60% kcal lard for 3-4 months to induce obesity and hepatosteatosis, as confirmed by *in vivo* MRS measurements on a clinical 3T scanner adapted with a dedicated animal coil.

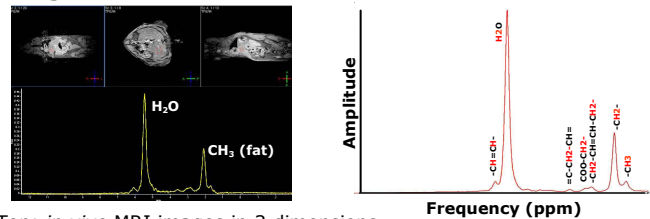


Thereafter the mice were matched based on body weight, liver fat by MRS and plasma lipids and glucose. The mice were fed the HFD alone (HFD control) or were treated with either rosiglitazone (10 mg/kg/d) or ezetimibe (3 mg/kg/d). 5 mice on a chow diet were included as a healthy control group. Effects on plasma lipid and glucose levels and liver lipid content were assessed after 4 weeks of treatment.

Ex vivo liver analyses were performed by histology, HPTLC, Magic Angle Spinning-NMR and photonic needle (diffuse optical spectroscopy) to compare with the data obtained *in vivo*.

Results

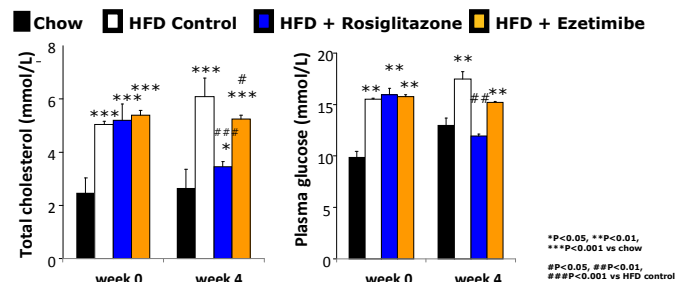
Liver fat can be measured accurately *in vivo* in mice using a clinical 3T MRI scanner



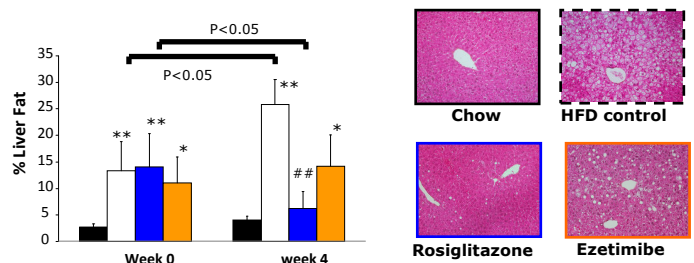
Top: *in vivo* MRI images in 3 dimensions

Bottom/right: *in vivo* MRS spectrum from voxel indicated in the MR images

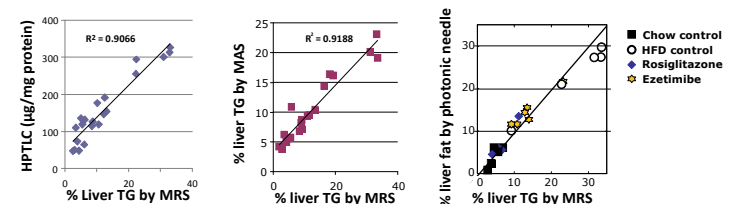
Rosiglitazone and ezetimibe improve plasma parameters



Rosiglitazone reduces and ezetimibe holds NAFLD



In vivo measurements correlate with *ex vivo* analyses



Conclusion

Liver lipids in mice can accurately be measured *in vivo* using a clinical 3T MR scanner

Rosiglitazone reduces hepatosteatosis, like in humans
 Ezetimibe inhibits disease progression

APOE*3Leiden.CETP mice on a HFD (60% lard kcal)
 -Develop the metabolic syndrome and NAFLD
 -Respond to anti-diabetic and hypolipidemic treatments

Data obtained *in vivo* highly correlate with *ex vivo* measurements:
 Histology, HPTLC, MAS-NMR, Photonic needle