Conclusion: Vitamin D supplementation seems to have an effect on the levels of apoptosis on histologic NASH but not advanced fibrosis. These data suggest that the protective effects of Vitamin D may be subject to a systemic damage threshold. Further research is warranted to elucidate the impact of Vitamin D on apoptosis in NAFLD.

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ROLE OF GROWTH HORMONE-SOCS2 AXIS IN THE DISSOCIATION BETWEEN HEPATOSTEATOSIS AND INSULIN RESISTANCE

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Hepatic steatosis is a prominent feature in growth hormone (GH)-deficient patients and hepatic GH receptor knockout mice. SOCS2, a GH-induced protein, attenuates hepatic GH signalling by inhibiting the JAK2-STAT5b axis. Here we investigated the role of SOCS2 in the development of diet-induced hepatic steatosis and insulin resistance. We demonstrated that SOCS2 knockout ($SOCS2^{-/-}$) mice are protected from high-fat diet (HFD)-induced hepatic steatosis. This phenotype is explained by the enhanced expression of genes involved in triglyceride (TG) synthesis coupled with increased hepatic TG secretion. In contrast, we found that HFD-triggered attenuation of systemic and hepatic insulin sensitivity was more marked in $SOCS2^{-/-}$ mice. Livers from the HFD-fed $SOCS2^{-/-}$ mice showed increased NFkB activity as well as elevated expression of genes for the inflammatory cytokines INF-g and IL-6. The latter effects were also observed in white adipose tissues. An inhibitory role of SOCS2 on Toll-like receptor 4 signalling was demonstrated in bone marrow-derived macrophages obtained from the $SOCS2^{-/-}$ and wild-type mice. In addition to an exacerbated inflammatory response, the HFD-fed $SOCS2^{-/-}$ mice showed increased obesity and TG deposition in muscle tissues, which further contributed to metabolic deterioration in these mice.
Conclusions: To our best knowledge, we are the first to provide evidence that SOCS2 plays an important role in regulating the response to high-fat dietary stress through actions that control hepatic steatosis and inflammation.

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NARINGENIN ALLEVIATES HIGH-FAT-DIET INDUCED HEPATIC DAMAGE BY REDUCING PRO-INFLAMMATORY CYTOKINES SYSTEMICALLY AND LOCALLY

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Background and Aims: Obesity is acknowledged as a risk factor for nonalcoholic fatty liver diseases (NAFLD), as well as the other chronic diseases (type 2 diabetes and atherosclerosis). Obesity induced chronic low-grade inflammation plays a pivotal role in the process of NADLD pathogenesis. Adipose tissue macrophages produce a significant proportion of the inflammatory factors induced by adipocyte. Previous studies have showed that naringenin, a natural flavonoid, exerted anti-inflammatory effect in acute inflammation animal model. Here, we determine whether naringenin enables to improve NAFLD by its anti-inflammation effect.
Methods: We established a high-fat-diet induced obesity mice model with or without naringenin supplementation for 40 weeks and the physiological status were recorded twice a week. After sacrifice serum and tissue were collected and stored in −80°C. Serum FFAs and cytokines were detected by biochemical methods and ELISA. Real-time qPCR and western blot were employed to investigate the expression of tissue related inflammatory cytokines and mediators. Finally adipose-infiltrated macrophages markers were detected by IHC.
Results: The data showed naringenin significantly alleviated obesity induced hepatic damage and effectively reduced circulating and local (hepatic and adipose) pro-inflammatory cytokines level, such as TNF-α, IL-6, MCP-1, IL-1β, Leptin and Resistin. Serum FFA levels and visceral adipose infiltrated M1 macrophages significantly reduced in the naringenin supplemented mice compared to high-fat-diet group.
Conclusions: Naringenin treatment could ameliorate high-fat-diet mediated hepatic damage through relieving the systemic and the local inflammation.

10b. FATTY LIVER DISEASE: CLINICAL

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DECREASED SERUM LEVELS OF FIBROBLAST GROWTH FACTORS 19 AND 21 CORRELATE WITH SEVERITY OF TISSUE DAMAGE IN PEDIATRIC NAFLD

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Background and Aim: Non-alcoholic fatty liver disease (NAFLD) is one of most frequent liver diseases in children of industrialized countries. As the disease is generally silent, establishing a reliable and non-invasive diagnostic method for pediatric NAFLD represents a major challenge. Recently, it has been reported that fibroblast growth factor 19 (FGF19) and fibroblast growth factor 21 (FGF21) possess beneficial effects on *lipid* metabolism and hepatic steatosis in animal models. FGF19 and FGF21, under specific stimulation, can be released into the circulation and they function as endocrine factors. Therefore, we tested whether FGF19 and FGF21 serum levels, correlate with the metabolic profile and histological features in a large well-characterized cohort of children with NAFLD.
Methods: A total of 80 consecutive children with biopsy-proven NAFLD (48 males and 32 females, mean age 9.9±4.8 years) and 25 control subjects (15 males and 10 females, mean age 10.3±5.2 years), seen at our Centre from November 2008 to September 2011, were included in this study. Serum levels of FGF19 and FGF21 were determined by enzyme-linked immunosorbent assay (ELISA). Klotho receptor expression was evaluated by immunofluorescence in 10 of 25 controls and in 30 of 80 NAFLD patients.
Results: Our data demonstrated that, in children with NAFLD, serum levels of FGF19 and FGF21 were significantly lower (64.1 pg/ml and 73.44 pg/ml, respectively) ($p < 0.001$) than those observed in control subjects (208.5 pg/l and 190.65 pg/ml, respectively) ($p < 0.01$). Interestingly, decreased serum levels of FGF19 and FGF21 were significantly associated to high NAFLD activity score ($p < 0.001$) and with fibrosis score ($p < 0.001$). Furthermore, since FGF19 and FGF21 signaling requires Klotho family proteins, as cofactors to determine specific metabolic activities, we also studied Klotho hepatic expression by immunofluorescent analysis. NAFLD children displayed a decreased hepatic expression of Klotho receptors with respect to controls.
Conclusions: As FGF19 and FGF21 expression inversely correlates with liver damage in paediatric NAFLD, we believe that both can be used as potential novel non-invasive biomarkers in these subjects.