The growth hormone - insulin like growth factor I system in early non-alcoholic fatty liver disease: from an animal model to a pediatric cohort.

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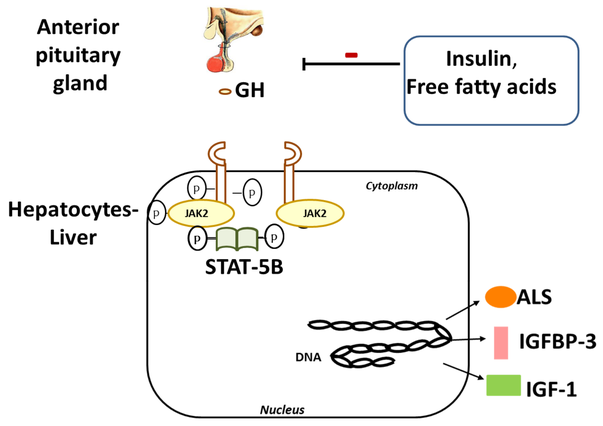
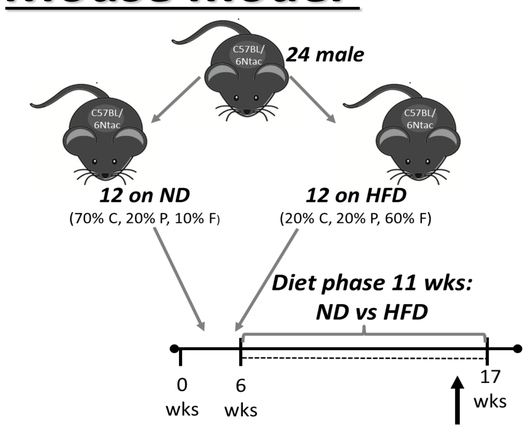
Background and Aims

Non-alcoholic fatty liver disease (NAFLD) represents one of the most common obesity complications. Steatohepatitis (NASH) is associated with lower plasma IGF-1 and IGFBP-3, however no data are available regarding the GH-IGF-I axis in simple hepatic steatosis in children. We aimed to investigate the GH-IGF-1 pathway in a diet induced animal model of liver steatosis and in a human cohort of obese and lean children.



Methods and Results

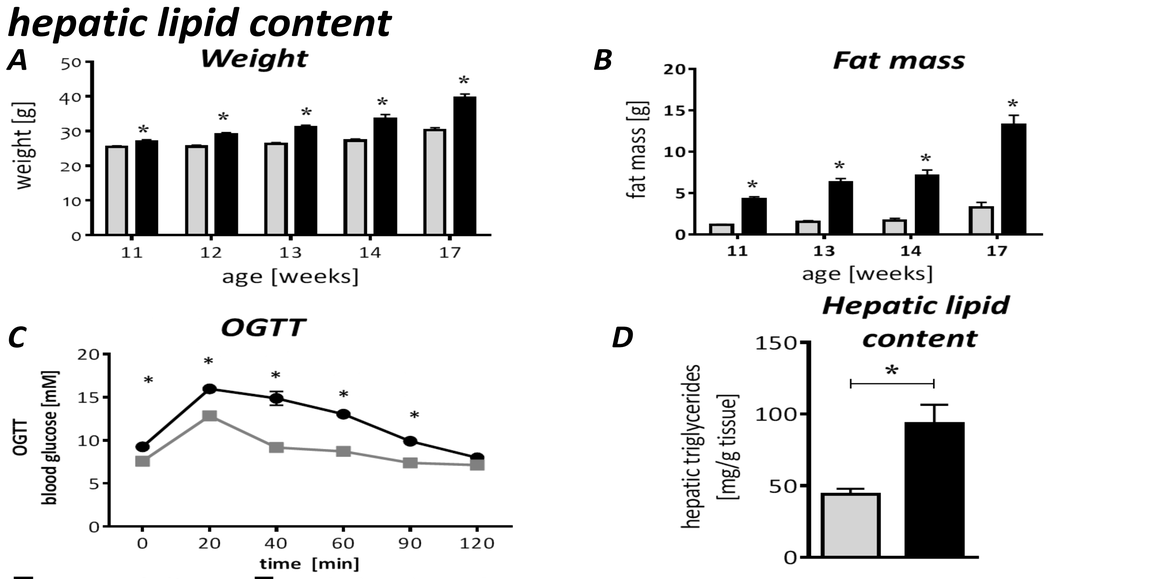
Mouse model



C57BL/6 mice were fed with a standard diet (ND) (12) or with a high fat diet (HFD) (n=12) for 11 weeks.

The mouse model was provided by the University of Copenhagen, in collaboration with prof J. Treebak

Effect of high fat diet on weight gain, glucose metabolism and hepatic lipid content

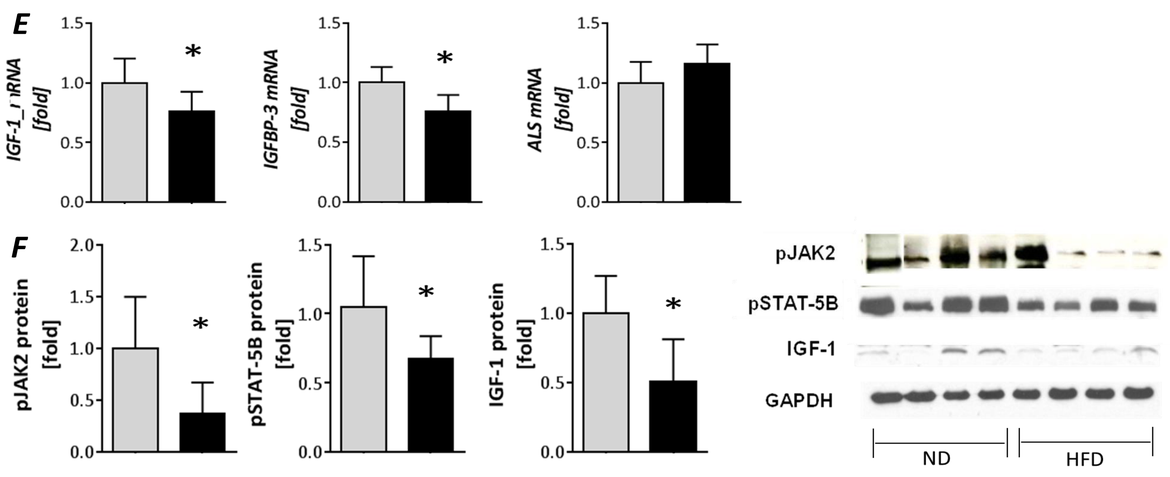


Normal diet High fat diet *= p<0.05

HFD mice gained weight and increased fat mass compared to ND mice. *(Fig A and B).*

HFD induce an impairment of glucose metabolism and an increase in hepatic lipid content compared to ND. *(Fig C and D)*

Effect of high fat diet on GH-IGF-1 axis



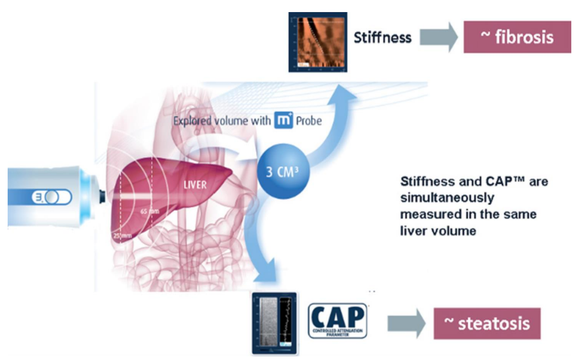
Normal diet High fat diet *= p<0.05

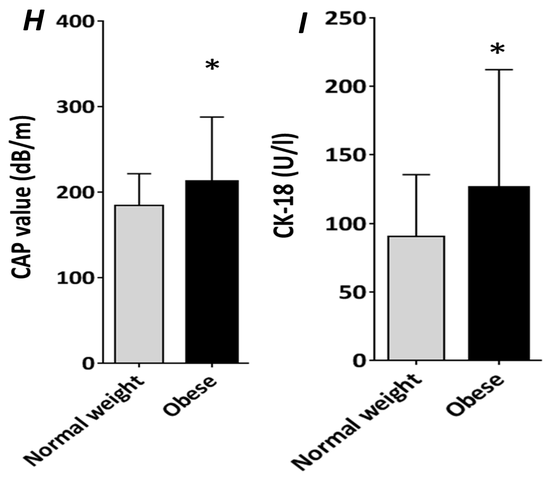
A lower expression of hepatic pSTAT-5B, pJAK2 and IGF-1 (-1.56, -2.7 and -1.9-fold) was found in HFD compared to ND mice. (*Fig E and F)*

Pediatric cohort

	Lean Children (88)	Obese Children (77)	p
Characteristcs of study population			
Age (years)	13.06±2.82	12.28±2.71	0.201
Gender	46M/42F	36M/41F	0.498
BMI-SDS	-0.01±0.93	2.18±0.55	<0.0005
Glucose metabolism			
Glucose (mmol/l)	4.75±0.30	4.78±0.34	0.702
Insulin (pmol/l)	62.4±28.1	95.4±34.4	0.002
HOMA-IR	1.86±0.95	3.04±2.30	<0.0005
WBISI	5.72±3.01	3.57±1.75	<0.0005
Lipid metabolism and liver function			
Total Cholesterol (mmol/l)	4.02±0.68	4.02±0.65	0.911
HDL Cholesterol (mmol/l)	1.56±0.33	1.36±0.28	0.0005
LDL Cholestserol (mmol/l)	2.31±0.67	2.39±0.57	0.350
Triglycerides (mmol/l)	0.76±0.30	0.92±0.44	0.016
ALT (µkat/L)	0.29±0.10	0.38±0.18	0.032
AST (µkat/L)	0.44±0.15	0.44±0.14	0.951

Evaluation of hepatic steatosis

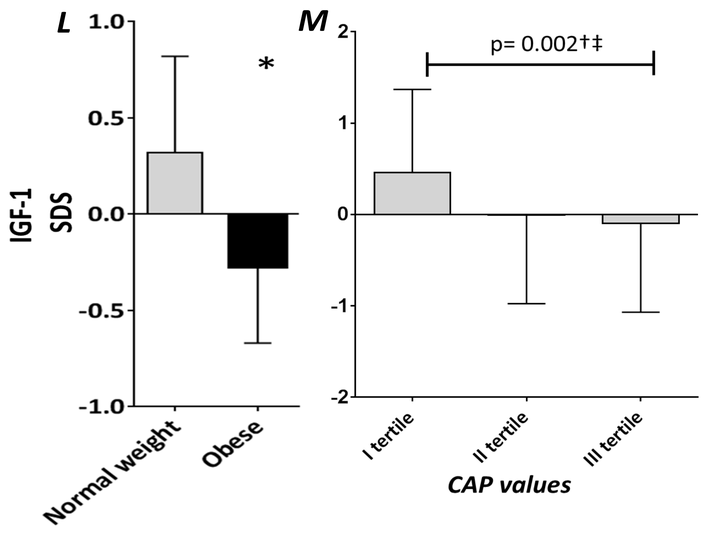




Normal weight Obese *= p<0.05

Obese children presented higher CAP and CK-18 values compared to normal weight children (p<0.005), indicating a steatotic phenotype. (*Fig H and I)*

IGF-1 levels in the pediatric cohort



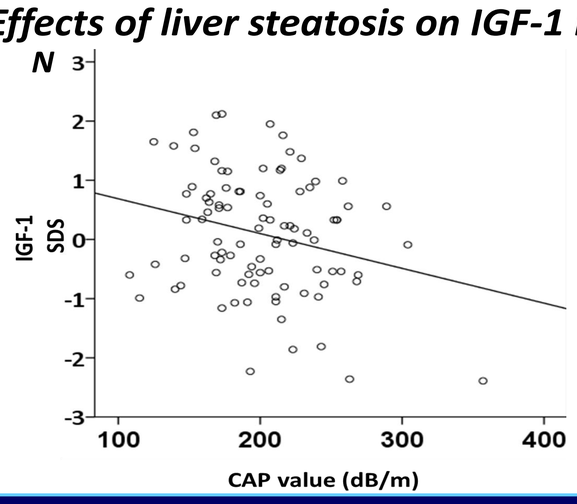
Obese subjects presented lower IGF-1 compared to controls (p=0.007). (*Fig L)*

IGF-1-SDS decreased across CAP values tertiles. (*Fig M)*

Normal weight
Obese
*= p<0.05
†= I *vs* II tertile
‡= I *vs* III tertile

I tertile: <177 dB/m
II tertile: 177-217 dB/m
III tertile: >217 dB/m

Effects of liver steatosis on IGF-1 levels in children



An inverse and significant correlation was found between CAP values and IGF-1-SDS (p= 0.014, r=-0.254). (*Fig N)*

Conclusion

The GH-IGF-1 axis is already impaired in early NAFLD. In particular, IGF-1 could be an early marker to define the hepatic steatotic phenotype.

Abbreviation: ND: Normal diet; HFD: High fat diet; OGTT: Oral glucose tolerance test; IGF-1: Insulin like growth factor-1; STAT-5B: Signal transducer and activator of transcription-5B; pSTAT-5B: phosphor-Signal transducer and activator of transcription-5B; pJAK-2: phosphor-Janus Kinase-2; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; CAP: controlled attenuated parameters; CK-18: cytokeratin 18

References

Rinella ME, JAMA 2012; Chia DJ et al., Mol Endocrinol 2014; Penke et al, Mol Cell Endocrinol 2015;

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