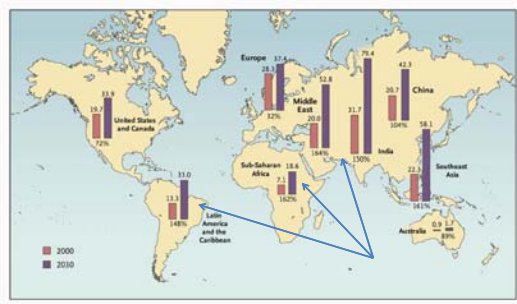


NAFLD AND TYPE 2 DIABETES

Sonia Caprio, MD

STOPNASH- Symposium on the Origin and Pathways of Nonalcoholic Steatohepatitis
Washington 7, 2015

Global Projection of Diabetes

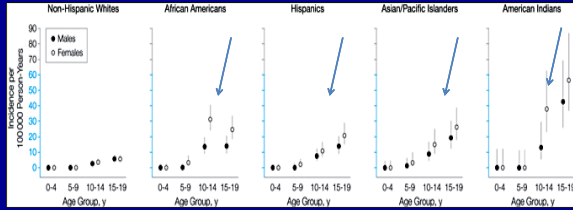


Hossain P et al. N Engl J Med 2007;356:213-215 THE NEW ENGLAND JOURNAL OF MEDICINE

The Epidemic of Childhood Obesity and the Rising Number of Kids with T2DM



Incidence of Type 2 Diabetes Mellitus by 5-Year Age Groups, Sex, and Race/Ethnicity, 2002-2003



The Writing Group for the SEARCH for Diabetes in Youth Study Group, JAMA 2007;297:2716-2724.



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T2D and NAFLD: Are they related ?

T2D and NAFLD in adults

- NAFLD is a frequent finding in adult patients with T2D due to their common underlying pathogenic mechanism of insulin resistance (Cusi et al 2009).
- The prevalence of NAFLD in T2D patients ranges broadly between 43% and 94%.
- The presence of T2D is an independent predictor of advanced fibrosis in NAFLD (Lomba 2015)

OBJECTIVES

- ✓ Present data on the association between Fatty Liver and glucose dysregulation in obese adolescents
- ✓ Discuss the important role of the liver in the insulin resistance seen in obese adolescents

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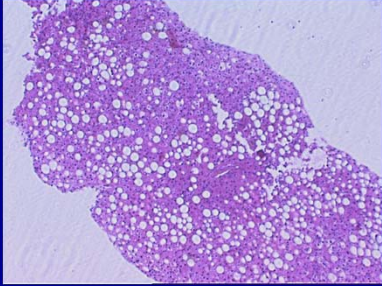
Might Fatty Liver Disease Be A Prelude to the Development of T2D In Obese Adolescents?

Metabolic Phenotype of a young girl with Non-Alcoholic Steatohepatitis (NASH) and T2DM

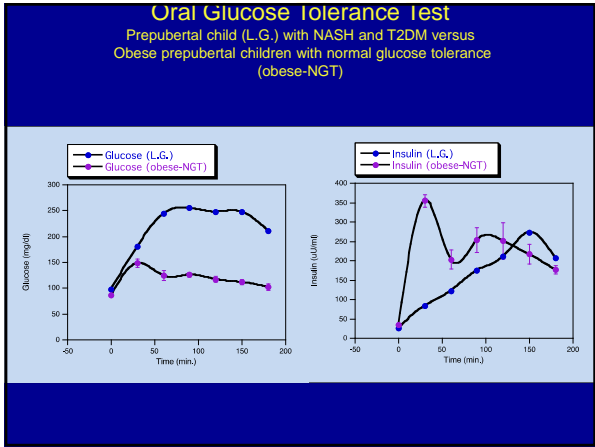
L.G.	DOB 12-10-91
• Height	148 cm
• Weight	58 kg
BMI	26.2 kg/m ²
% fat	47 % (BIA)
	reference range
• ALT	206 U/L (0-35)
• AST	211 U/L (0-35)
• GGT	163 U/L (7-33)
• Fasting Glucose	154 mg/dl
Fasting Insulin	34 µU/ml
• Triglyceride	264 mg/dl
HDL -CHOL	28 mg/dl

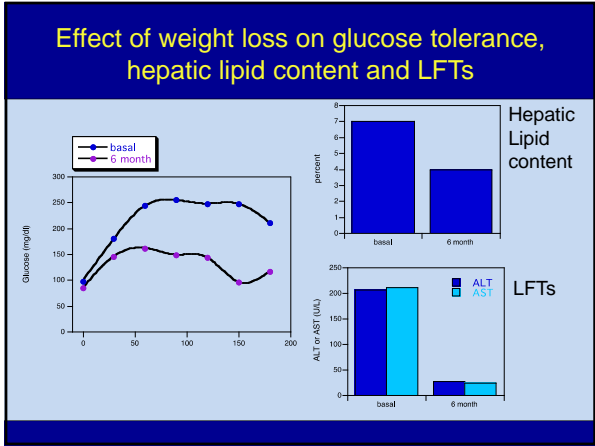
Liver Needle Biopsy

Severe macrovesicular steatosis
Bridging fibrosis (stage III)



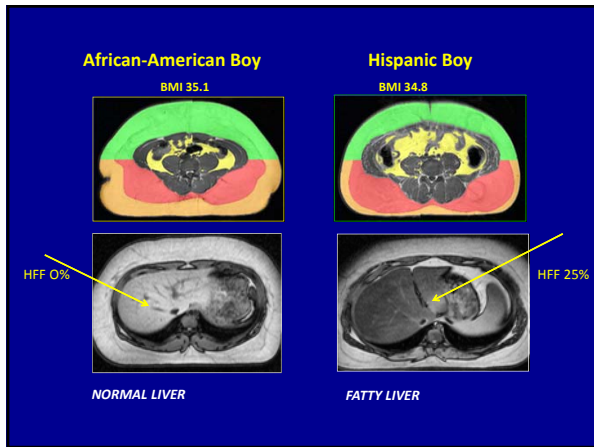
L.G.
DOB 12/91



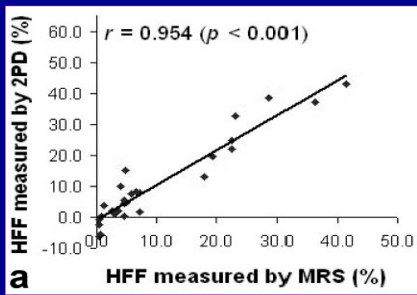


How Do We Measure Fat Content in The Liver?

- Liver Biopsy
- 1H-NMR
- Fast- MRI



Validation of the two Point Dixon Method (2PD) against Hepatic Fat Content measured by ¹H-NMR in 34 obese and lean adolescents.



Kim H, et al. Magn Reson. Med. 2008; 59:521-27

Glucose Dysregulation and Fatty liver in obese adolescents : Is there a link?

• 118 obese adolescents with similar degree of overall adiposity

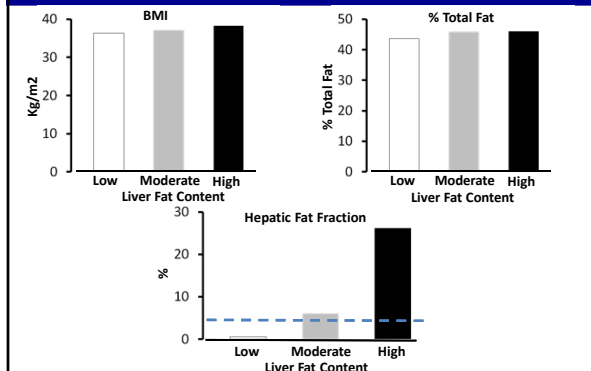
• Oral Glucose Tolerance Test

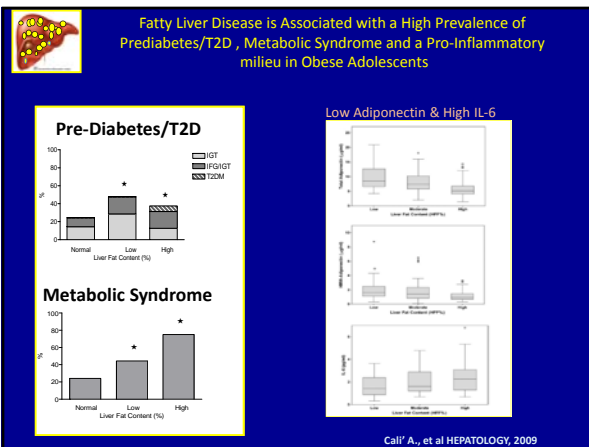
• MRI for assessing Abdominal Fat Distribution and Hepatic Fat Content

• Body Composition by DEXA

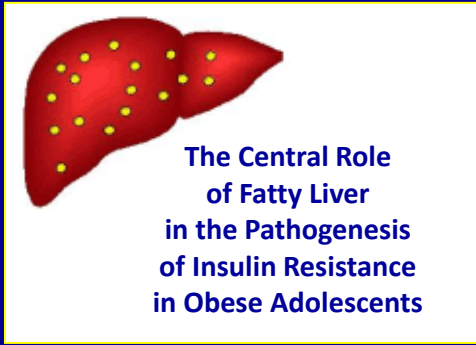
Cali et al HEPATOLOGY 2009

Anthropometric Phenotypes According to tertiles of Liver Fat Content in 118 Obese Adolescents





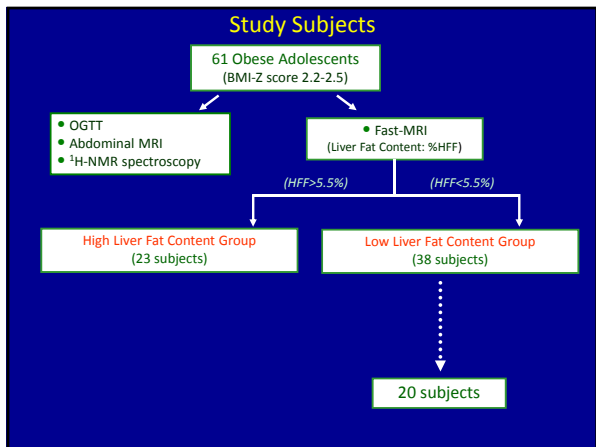
Cali A., et al HEPATOLOGY, 2009



D'Adamo E et al, Diabetes Care 2011

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**Does Intrahepatic Fat
Independent of Visceral and
IMCL Contribute
to the Development of
Insulin Resistance?**



Metabolic Studies

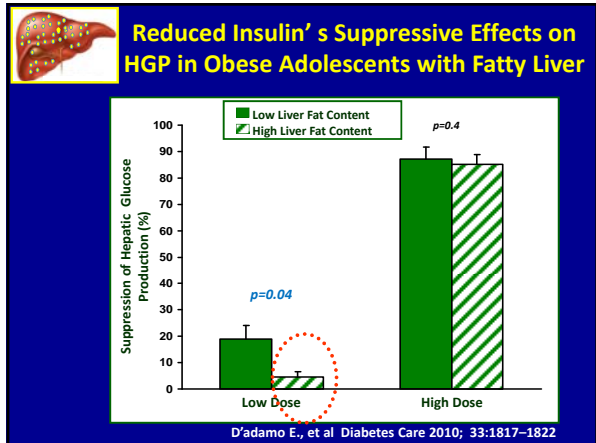
❖ Hyperinsulinemic-euglycemic clamp

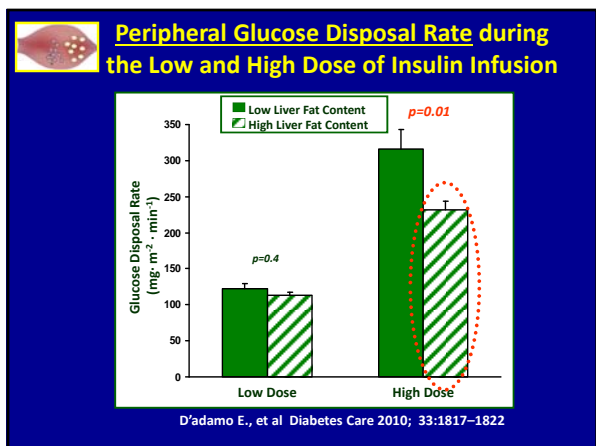
- Whole-body insulin sensitivity was measured by 2 step hyperinsulinemic euglycemic clamp:

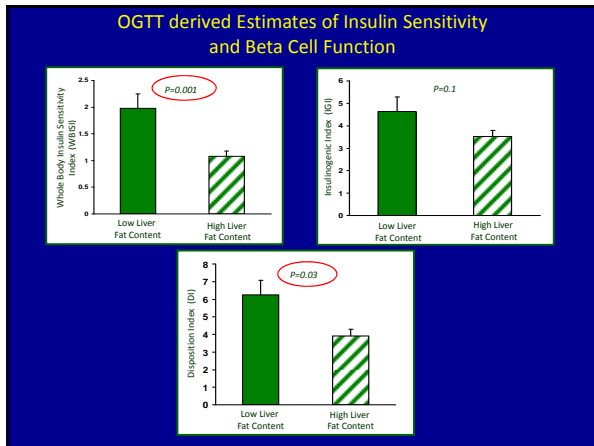
Low Dose Insulin ($4 \text{ mU} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$)

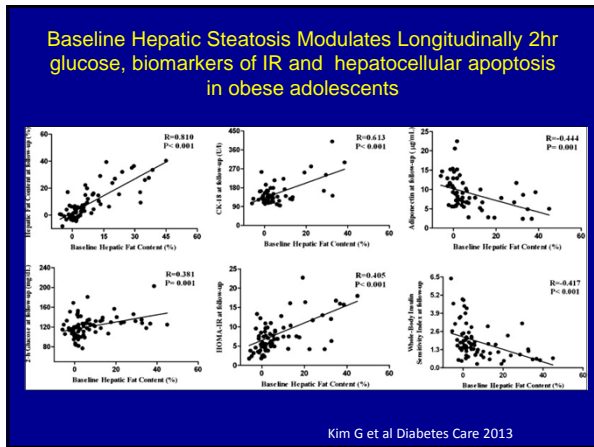
High Dose Insulin ($80 \text{ mU} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$)

- A primed continuous infusion of 6,6-deuterium glucose and of ^3H -glycerol were used to quantify insulin's effects on glucose and glycerol turnover.









Summary

Independent of Visceral Fat and IMCL, Intrahepatic Fat Accumulation is associated with:

- ❖ impaired insulin action in the liver and in the muscle;
- ❖ early defects in beta cell function
- ❖ a trend towards lower suppression of glycerol turnover during the low insulin dose.
- ❖ low adiponectin levels

Key Findings

- ❖ Fatty liver is associated with prediabetic phenotypes, and thus may be considered a strong risk factor for T2DM, independent of overall obesity in youth

"The Yale Team"

Mary Savoye



Melissa Shaw



Bridget Pierpont

Nicola Santoro

Romy Kursawe