NAFLD AND TYPE 2 DIABETES

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Global Projection of Diabetes


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


? 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 (Loomba 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

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

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

L.G. DOB 12-10-91
• Height 148 cm
• Weight 58 kg
• BMI 26.2 kg/m²
• % fat 47% (BIA)

• ALT 216 U/L (0-35)
• AST 231 U/L (0-35)
• GGT 163 U/L (7-50)
• Fasting Glucose 154 mg/dl
• Fasting Insulin 34 µU/ml
• Triglyceride 264 mg/dl
• HDL CHOL 26 mg/dl
Liver Needle Biopsy
Severe macrovesicular steatosis
Bridging fibrosis (stage III)

DOB 12/91

Oral Glucose Tolerance Test
Prepubertal child (L.G.) with NASH and T2DM versus
Obese prepubertal children with normal glucose tolerance
(obese-NGT)

Effect of weight loss on glucose tolerance,
hepatic lipid content and LFTs
How Do We Measure Fat Content in The Liver?

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

African-American Boy

BMI 35.1

HFF 25%

Hispanic Boy

BMI 34.8

HFF 25%

NORMAL LIVER

FATTY LIVER

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

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

1. 118 obese adolescents with similar degree of overall adiposity
2. Oral Glucose Tolerance Test
3. MRI for assessing abdominal fat distribution and hepatic fat content
4. Body Composition by DEXA

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

Fatty Liver Disease is Associated with a High Prevalence of Pre-diabetes/T2D, Metabolic Syndrome and a Pro-inflammatory milieu in Obese Adolescents
Increasing fasting and 2hr glucose levels across tertiles of Hepatic Fatty content and ALT levels: The Yale Pediatric NAFLD Cohort

Santoro N & Caprio S: Personal data

FGF-21 levels in Obese Youth: Effects of Fatty liver

Gianini C et al; JCEM 2013

Key Findings

- Fatty liver is associated with prediabetic phenotypes, and thus may be considered a strong risk factor for MS, independent of overall obesity in youth
The Central Role of Fatty Liver in the Pathogenesis of Insulin Resistance in Obese Adolescents

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

Study Subjects
- 61 Obese Adolescents (BMI-Z score 2.2-2.5)
  - OGTT
  - Abdominal MRI
  - $^1$H-MR spectroscopy
  - Fast-MRI (Liver Fat Content: %HFF)
  - (HFF>5.5%) (HFF<5.5%)
- High Liver Fat Content Group (23 subjects)
- Low Liver Fat Content Group (38 subjects)
- 20 subjects
Metabolic Studies

- **Hyperinsulinemic-euglycemic clamp**
  - Whole-body insulin sensitivity was measured by 2-step hyperinsulinemic euglycemic clamp:
    - Low Dose Insulin (4 mU · m⁻² · min⁻¹)
    - High Dose Insulin (80 mU · m⁻² · min⁻¹)
  - A primed continuous infusion of 6,6-deuterium glucose and of \(^{2}H_{5}\)-glycerol were used to quantify insulin’s effects on glucose and glycerol turnover.

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**Reduced Insulin’s Suppressive Effects on HGP in Obese Adolescents with Fatty Liver**

- Low Liver Fat Content
- High Liver Fat Content

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**Peripheral Glucose Disposal Rate during the Low and High Dose of Insulin Infusion**

- Low Liver Fat Content
- High Liver Fat Content
Baseline Hepatic Steatosis Modulates Longitudinally 2hr glucose, biomarkers of IR and hepatocellular apoptosis in obese adolescents

Kim G et al Diabetes Care 2013

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