"Fatty acid dysregulation in NAFLD"

STOPNASH
Symposium on **t**he **O**rigins and **P**athways of
Nona**l**coholic **S**teato**h**epatitis
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Studying the fasting to fed state transition

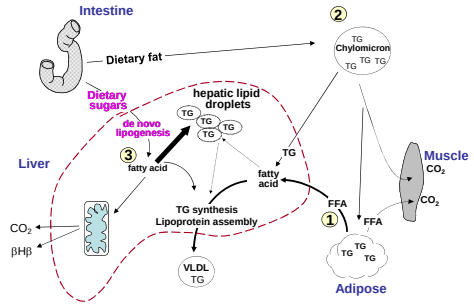
The ability to appropriately fast is maintained in obesity and insulin resistance.

The metabolism that causes disease occurs at the transition from the fasting to fed state.

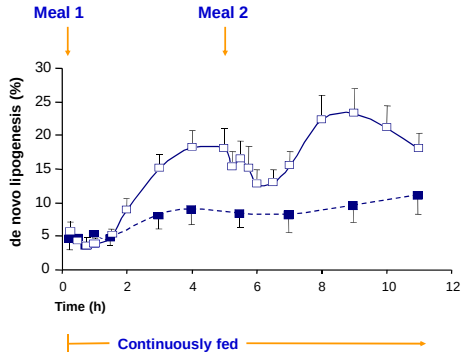
Outline

- **Lipogenesis in health subjects and those with insulin resistance**:
  - **effect of sugars**
  - **circadian patterns**
- **Is liver energy metabolism limited in NAFLD?**
- **Changes in fatty acid fluxes with weight loss in NAFLD**
- **A case study of weight loss**

Liver-TG fatty acid sources, fluxes, and fates

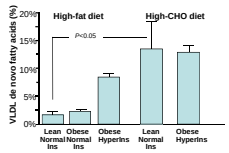


Liver's synthesis of de novo fatty acids from dietary CHO

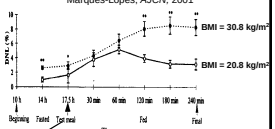


Elevated lipogenesis: Obesity, insulin resistance, diabetes

Schwarz, *AJCN*, 2003

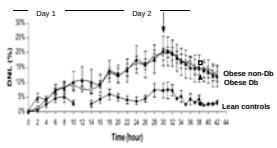


Marques-Lopes, *AJCN*, 2001

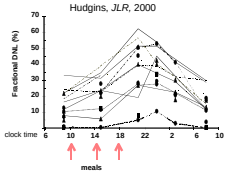


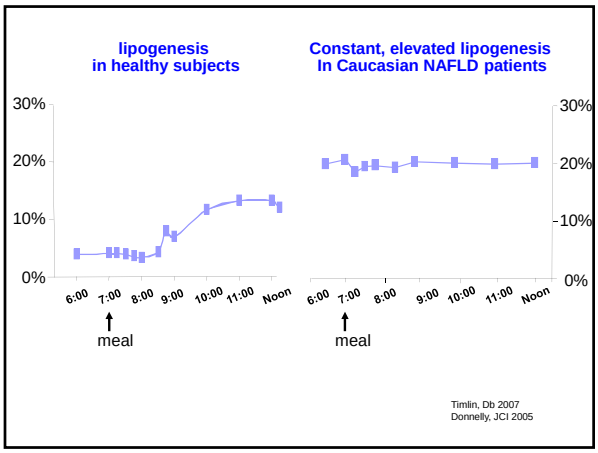
80% CHO test meal
53% sucrose
27% lactose

Vedala, *JLR*, 2006



Hudgins, *JLR*, 2000





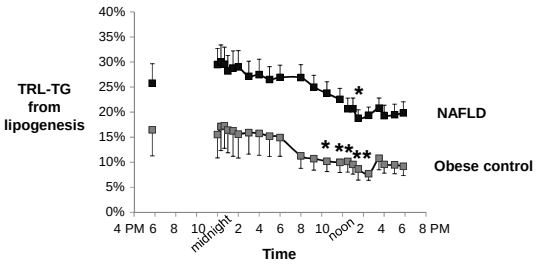
NAFLD Clinical Trial

- **A study of subjects with a wide range of liver fat and insulin sensitivities**
- **To determine the relationships between nutrient metabolism during the fasted and fed states and liver (and whole body) fatty acid flux.**
- **Determine the metabolic mechanisms that reduce liver fat during weight loss.**

Subject characteristics

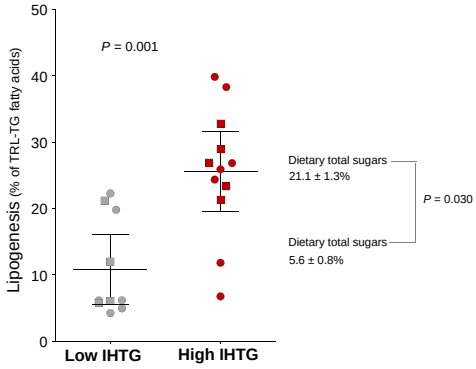
	Low IHTG	High IHTG	*P*-value
No of subjects	11	13	
IHTG (%)	3.1 ± 2.9	18.4 ± 3.6	<0.001
BMI (kg/m²)	35.3 ± 7.8	34.9 ± 5.3	0.443
Body weight (kg)	102.9 ± 21.8	92.2 ± 17.5	0.193
Body fat (%)	39.7 ± 10.5	39.2 ± 6.8	0.442
FFA (mmol/L)	0.57 ± 0.15	0.66 ± 0.12	0.106
TG (mg/dL)	110 ± 50	134 ± 54	0.137
Glucose (mg/dL)	91.3 ± 8.8	98.0 ± 14.4	0.195
Insulin (mU/L)	8 ± 4	11 ± 4	0.049
HOMA	1.67 ± 0.79	2.63 ± 1.10	0.024
SI (10^{-4} * min $^{-1}$ per μU/mL)	3.1 ± 1.4	2.2 ± 1.4	0.136
ALT (U/L)	47 ± 36	69 ± 45	0.239

Higher de novo lipogenesis in NAFLD. Less suppression with fasting.



* Significantly lower than 1 AM

de novo lipogenesis and dietary sugars



Outline

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  - circadian patterns
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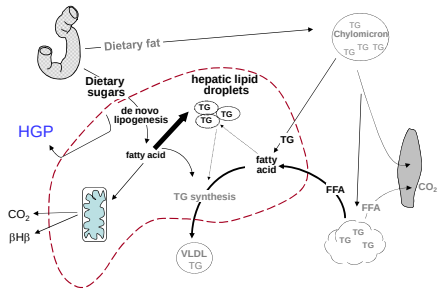
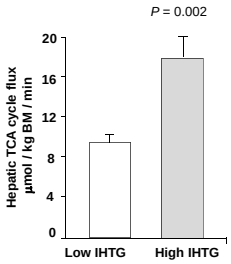
The role of mitochondrial energy metabolism



Current controversy

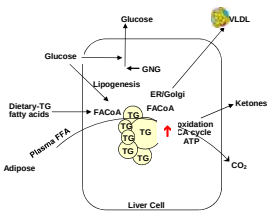
Few mitochondria in NAFLD?
More mitochondria, but dysfunction?
ROS?

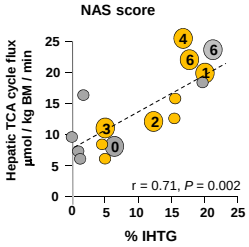
Liver TCA cycle activity



Sunny/Parks, *Cell Metabolism*, 2011

Is mitochondrial activity limiting in NAFLD?



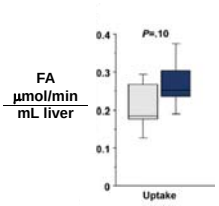


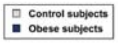
Sunny/Parks, *Cell Metabolism*, 2011

Fasting hepatic substrate fluxes in humans

Iozzo, *AJG*, 2010

^{11}C-palmitate infused, quantitated by PET





Yes, energy generation is limited

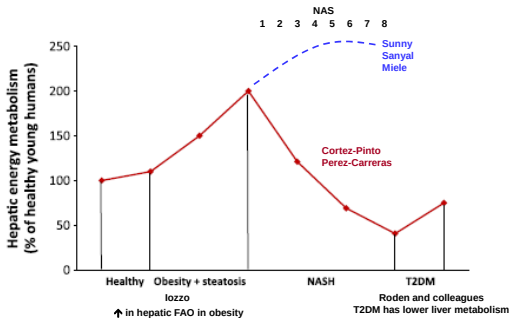
Cortez-Pinto	^{31}P-MRS	↓ ATP recovery after fructose in biopsy-proven NASH compared to leaner controls
Perez-Carreras	in vitro ETC, biopsy	mito resp chain activity lower in NASH
Schmid	^{31}P-MRS	Flux thru ATP syn lower in T2DM (not NAFLD)

No, energy metabolism is not limited

Sanyal	in vitro βox from biopsies	↑ in NASH
Sunny	U-^{13}C-propionate, NMR	↑ in hepatic TCA cycle activity
Iozzo	^{13}C-palmitate, PET	↑ in hepatic FAO in obesity (not NAFLD)
Miele	^{13}C-8:0 breath test	↑ cumulative ox in NASH compared to controls

Plasma βHB concentrations as a biomarker? just don't do it

Hepatic energy metabolism



Koliaki and Roden, *Mol Cell Endo,* 2013

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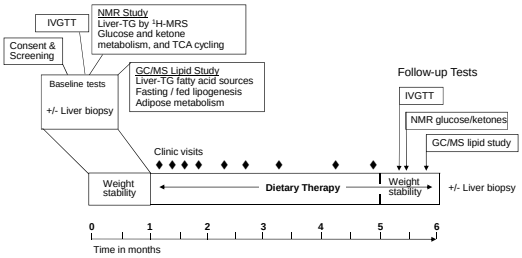
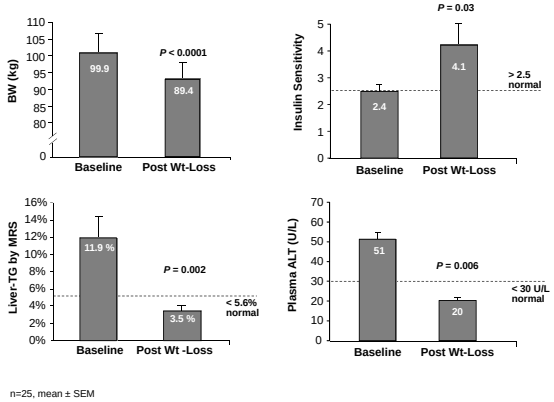
Phase 1
Baseline metabolic tests

Phase 2
Weight loss and follow-up

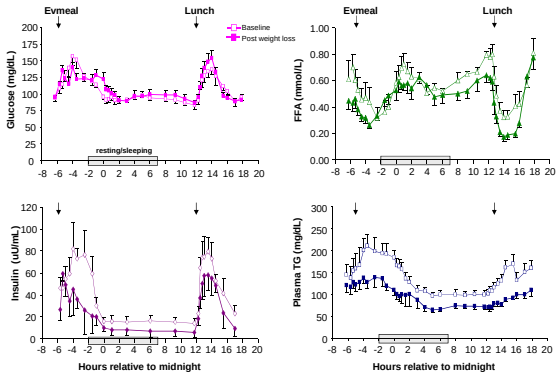


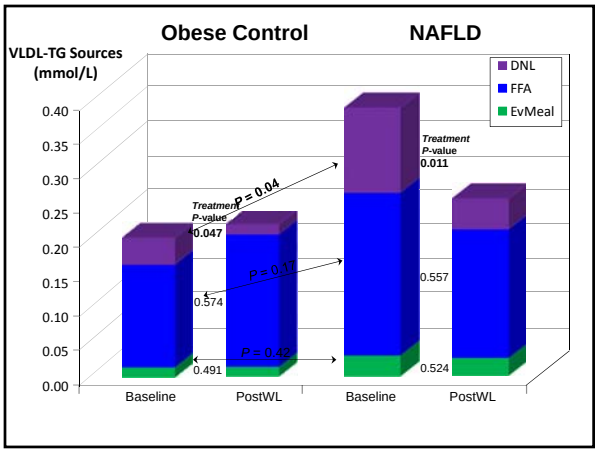
Changes due to caloric restriction



n=25, mean ± SEM

Fasting and fed concentrations





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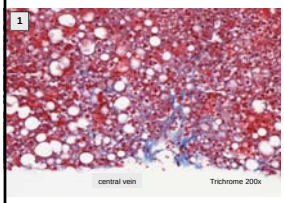
Case Study: Subject #8

33 yo Hispanic female

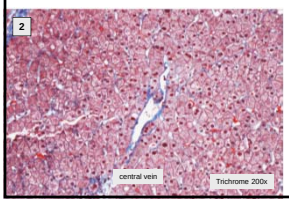
Body weight = 68.8 kg	Glucose = 93 mg/dL
BMI = 31.8 kg/m^2	Insulin = 11 mU/L
Body fat = 40.7 %	HbA1c = 6.2 %
W:H = 0.99	Ins Res (DI 992)
Liver fat = 27.3 %	ALT = 63 mU/L

Subject #8 Histology



1. Baseline Histology Trichrome 200x
Mild pericellular fibrosis adjacent to central veins.
Ballooning degeneneration of hepatocytes.

	Baseline		Post-Wt loss
Body weight:	68.8	→	61.5 kg
Liver fat:	27.3%	→	1.8%
Plasma ALT:	63	→	11 U/L
Nash Score:	1	→	0
Ins Res (DI 992)		→	Ins Res (DI 947)
Plasma TG	167	→	86 mg/dL



2. Follow-up Histology Trichrome 200x
Healthy liver demonstrating resolution of steatosis and fibrosis.

Summary

Metabolic derangments of the fasted to fed state transition lead to the development of disease.

These preliminary data suggest that the metabolic environment of the liver in metabolic syndrome is characterized by an increase in lipogenesis from sugars.

Weight loss significantly lowers liver fat content. It can do so by improving all of these pathways to reduce the burden of fatty acids in the liver.

Of the 22 outcomes measured, the primary improvement in patients regressing their liver fat was a significant reduction in hepatic de novo lipogenesis.

Parks Lab moto, "Panta Rei"
~ all things are in flux ~

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Environmental weight loss strategy