Restriction of dietary carbohydrates: Impact on metabolism

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Overview: Carbohydrate (CHO) restriction

- Hepatic metabolism
  - ↑ketone production
  - ↓TG, ↑HDL-C, ↓DNL
- Energy expenditure and fuel metabolism
  - ↑Energy expenditure and fat oxidation
- Body composition
  - ↓Body fat with preservation of lean mass
  - ↓Ectopic fat (weight maintenance)
- T2D: ↓fasting and postprandial glucose and HbA1c
- Race/ethnicity-specific effects

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Human evolution

- Humans evolved to eat a low-carb diet
  - Hunter-gatherers
  - Meat, nuts, etc.
- Agriculture began 10,000 yr ago
- Low-carb diets are not "dangerous"
  - Protein consumption is not excessive
  - Ketones are a physiologically relevant fuel source that can be used by the brain (low O_2 requirement)
  - Not "ketoacidosis"
  - The liver makes glucose

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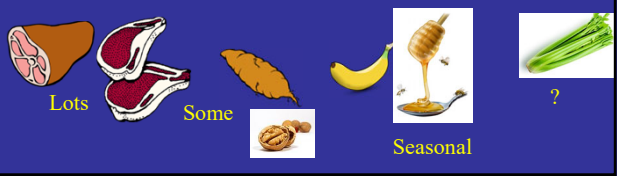
What we evolved to eat

- 35:65 Plant : animal (Paleolithic period)
- 40:30:30 %Fat:%Protein:%CHO
  - CHO as fermentable fiber
- Humans evolved to store fat
  - 12 kg fat (100,000 kcal)
  - 400-500 g glycogen (~1200 kcal)



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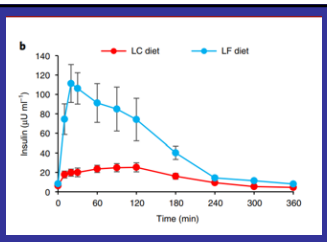
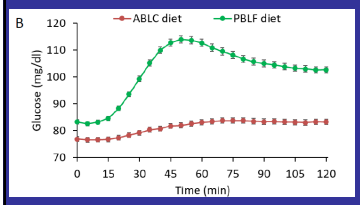
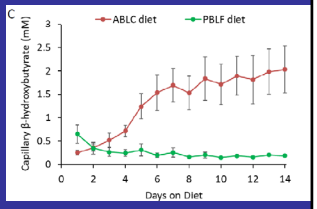
Low CHO vs low-fat diet in healthy adults



- High carb (75%)
- High fat (75%)
- 2-week crossover, wt mt





Hall et al. 2021. *Nature Med.* 27:344-53

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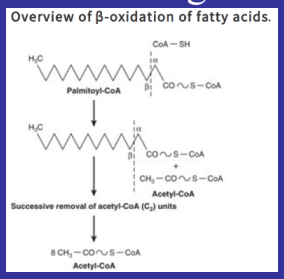
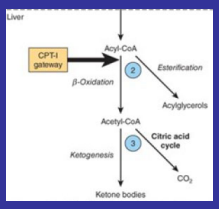
Fat oxidation and ketone production are regulated by INSULIN





Fate of acetyl CoA to ketones vs. oxidation (CO_2) is "titrated" so that ATP production from FFA remains constant despite changing serum concentrations.
CHO ingestion regulates substrate metabolism via INSULIN.

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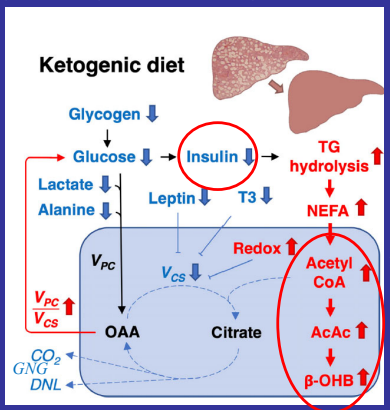
High circulating FFA and insulin together cause fatty liver



It's the process, not the ketones

Ketone production vs TCA cycle

The KD improves steatosis by markedly altering hepatic mitochondrial fluxes and redox state to promote partitioning of FA to ketogenesis rather than re-esterification and lipogenesis. Luukkonen et al. 2020. PNAS 117:7347

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Low carb diet interventions

Always more than just CHO restriction

- Removal of carbohydrates w/o replacement
  - Weight loss (-EB) and ketogenic
- Removal of CHO and addition of fat
  - Eucaloric and ketogenic
- Variable CHO restriction (10%-40%)

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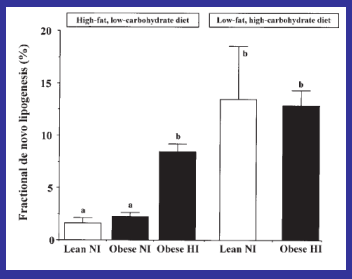
↓DNL with low-CHO (47%) diet when insulin is low



Schwartz et al. 2003 AJCN 77:43-50

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Effects of a very low-carbohydrate ketogenic diet (VLCKD) or a low-fat diet (LFD) for 12 weeks

Volek et al. 2008 *Prog Lipid Res* 47:307

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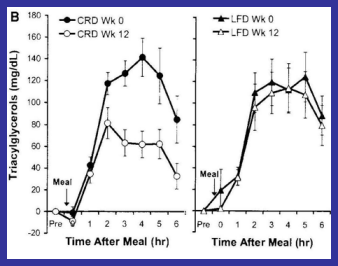
Low-CHO diet beneficial for lipids

Tightly controlled experiment involving 40 subjects with atherogenic dyslipidemia



Volek et al. 2009 *Lipids* 44:297

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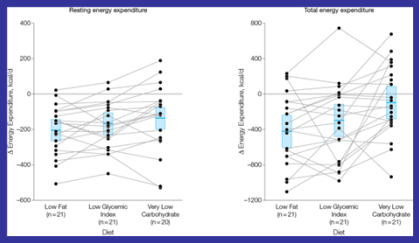
Greater energy expenditure during weight loss maintenance with low carb diet



Ebbeling et al 2012 *JAMA* 307:2627

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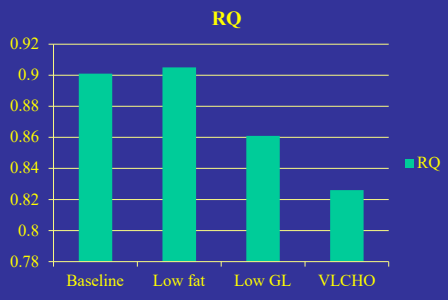
RQ decreases with CHO restriction (P<0.001)



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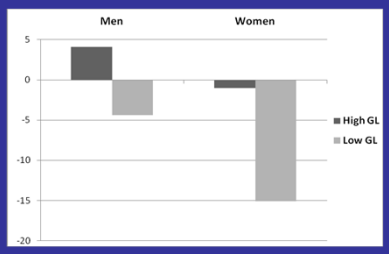
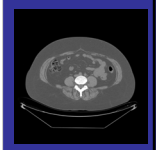
Greater loss of visceral fat on a eucaloric lower-CHO diet (P<0.01)





Goss et al., 2013 *Obesity* 21:1139.

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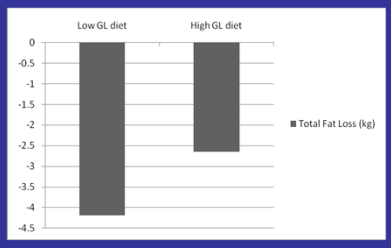
Greater fat loss on a hypocaloric lower-CHO diet (P<0.05)



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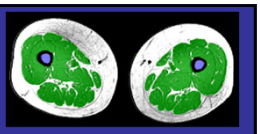
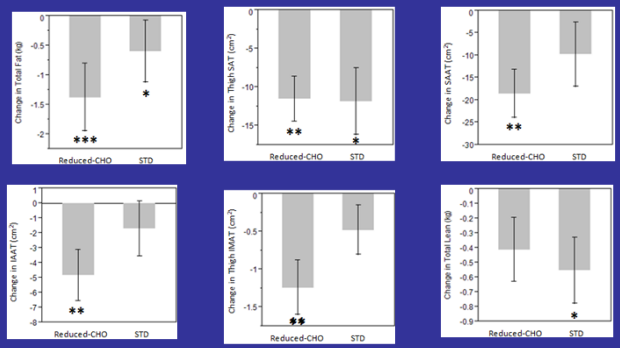
Favorable changes in body composition with lower-CHO diet





Goss *et al*. Metabolism. 2014 Oct;63(10):1257-64

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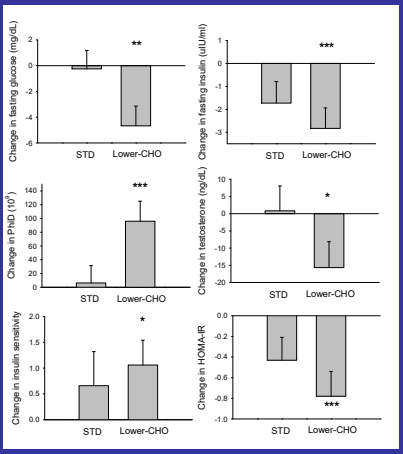
Results from paired *t*-test for changes within each diet



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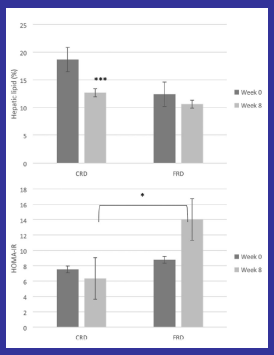
Reduced liver fat with 8 wk CHO restriction



Goss et al 2019 Ped. Obesity 2020;e12630.

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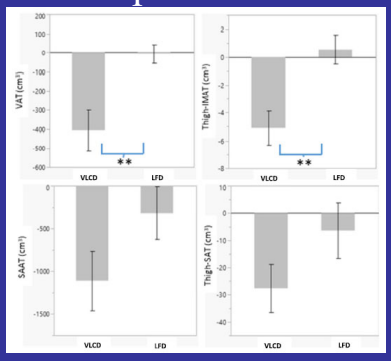
Reduced ectopic fat in older adults



8 weeks; Goss et al 2020 Nutrition and Metabolism 17:64

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Endocrine effects

- Vary with subject population, diet composition, and study design
- ↓Insulin ↑glucagon (↓insulin:glucagon)
- ↓Ghrelin
- ↓Leptin
- ↑24-h cortisol excretion
- ↓Thyroid axis (free T3, other measures)

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Low-CHO diet in T2D

- 46 patients with T2D
- Low CHO or Low-fat + Orlistat for 8 wk
  - ≤20g/d (energy not restricted)
  - <30% energy from fat (500-1000 kcal/d deficit)
    - Orlistat: 120 mg 3x/d
- Mayer SB et al. 2013 *Diabetes Obes Metab*. Aug 2. doi: 10.1111/dom.12191, epub ahead of print

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Greater decrease in BP, A1c, and medication use with low CHO *independent of weight loss*

	Low CHO		Low fat + Orlistat	
	Week 0	Week 8	Week 0	Week 8
Weight	117	109	125	117
Systolic BP	134	128**	125	130
Diastolic BP	85	80*	79	80
HbA1c	7.6	6.9*	7.6	7.7
% with 50% decrease in medication use		70.6%**		30.4%
LDL-C	105	104	100	90
HDL-C	35	38	35	36
TG	158	122	148	138

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Use of low-CHO diet in type 2 diabetes

- 10 obese patients
- 14 d low-CHO diet (21 g/d)
- Normalization of 24-h glucose
- Decreased HbA1c
- Improved insulin sensitivity
- Decreased TG and cholesterol
- Boden et al 2005 *Arch Int Med* 142:403

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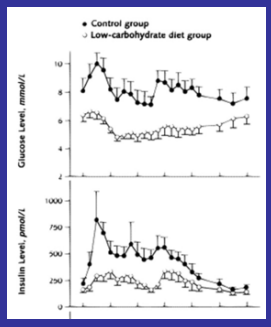

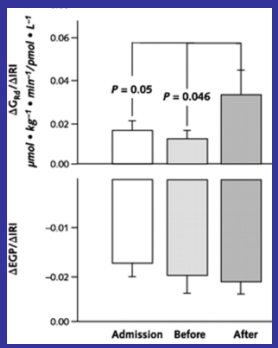

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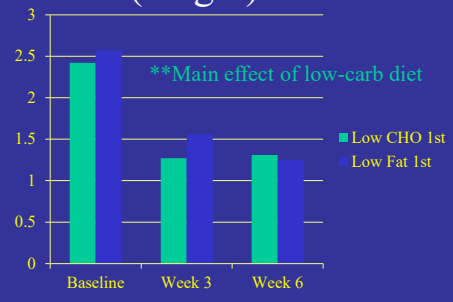
Lower in HGP in T2D with low-CHO (24 g/d) vs low fat



3-wk, low energy, cross-over; Gumbiner et al 1996 *AJCN* 63:110

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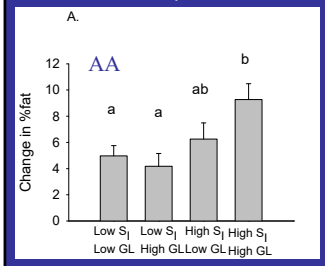
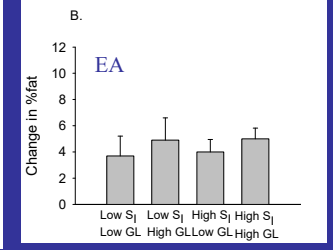
Race specificity of CHO sensitivity

*Insulin sensitivity
*Diet x insulin sensitivity





Gower et al. 2010. *Obesity* 18:1532

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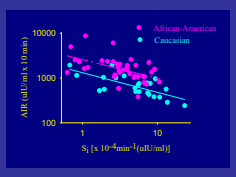
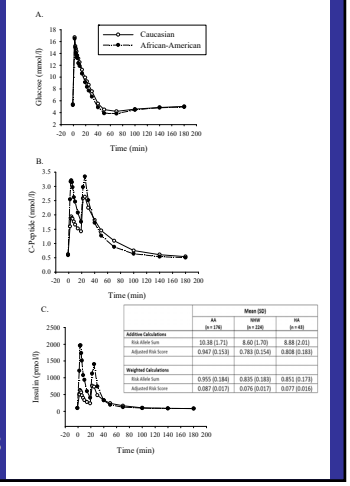
AA have greater beta-cell response; lower clearance



Gower et al. 2002 *JCEM* 87:2218



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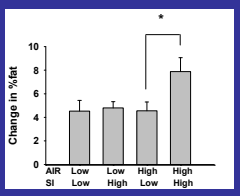
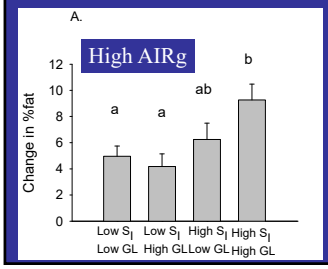
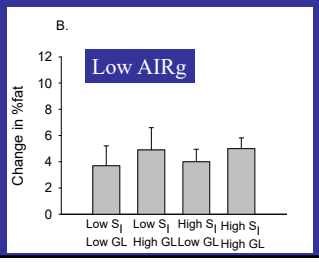
Interactive effects of S_I and AIRg







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Weight loss

Diet by ethnicity interaction?

	EA *n*=36	AA *n*=33
Sex (M/F)	18/18	13/20
BMI (kg/m^2)	31.8 ±3.7	33.2 ±4.7
Age (yr)	36.1 ±8.0	34.1 ±8.6
Weight (kg)	97.2 ±18.5	102.0 ±19.0
Fat mass (kg)	38.9 ±9.2	40.6 ±8.8
AIRg (uIU/ml x 10 min)	824 ±628	1415 ±917**

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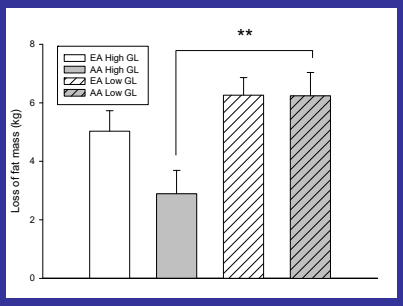
AA but not EA show diet difference in fat loss over 16 wk



Gower and Goss; *J Nutr* 2015, 145(1):177S-83S; Adjusted for S_I, baseline fat

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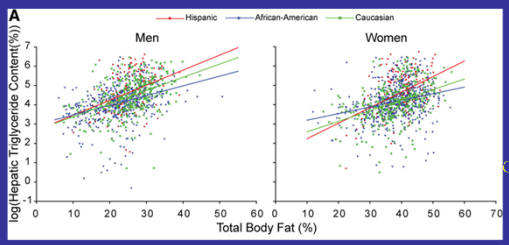
Higher liver fat among Hispanic Americans (PNPLA3 polymorphism)



Guerrero et al 2009 *Hepatology* 49:791

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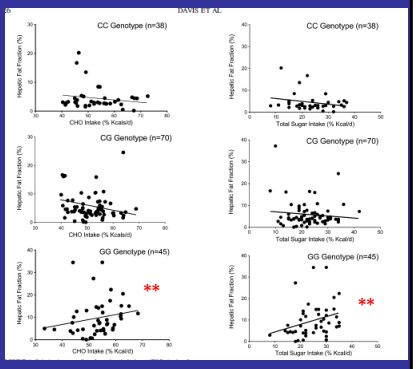
Hispanic: *PNPLA3* interaction with diet (CHO response element); C→G variant



Davis J et al. 2010. *AJCN* 92:1522

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Synthesis

- Ketogenic diets are useful for weight loss (hypocaloric)
  - Mobilization of fatty acids fuels the brain via ketones
- Ketogenic diets are therapeutic for individuals with type 2 diabetes
  - Conditions related to defective glucose metabolism or hyperinsulinemia
- CHO-restricted diets are beneficial for lean, healthy individuals
  - More favorable lipid profile and body composition
- CHO restriction may be particularly beneficial for
  - groups at elevated risk for metabolic diseases due to factors conferring sensitivity to carbohydrates (Black and Hispanic individuals)
- Glucose metabolism varies with activity level, physiological condition, genetic factors, and metabolic health
  - Consider the term "tolerance" vs "requirement" for dietary CHO

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Discussion points

- Carbohydrate quality
  - Grain-based heavily processed snack food ≠ tuber
- Energy balance
  - Dietary CHO excess less damaging during weight loss or energy balance?
- Interactive effects of dietary CHO, dietary fat, and EB
  - Dietary fat "bad" when consumed in excess with excess CHO, but "good" with KD and weight loss
- Do the benefits of CHO restriction differ with health status?
  - T2D with obesity vs healthy lean

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Acknowledgements

Postdoctoral Fellows

Adele Fowler
Sarah Deemer
Paula Chandler-Laney
Krista Casazza
Julian Muñoz
Jeannine Lawrence

Collaborators

Gary Hunter
Tim Garvey
Fernando Ovalle
Jose Fernandez
Amy Goss

Students

Valene Garr Barry
Sarah Tucker
Katie Couch
Amy Ellis
Jessica Alvarez
Nikki Bush
Tanya Hyatt
Radhika Phadke

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Acknowledgements

Core Facilities

Nikki Bush
Maryellen Williams
Cindy Zeng
Bob Petri
Heather Hunter
CRU Bionutrition

Staff

Laura Lee Goree, Jules Connelly, Caitlin Owens, Martrice Packer, Tena Hilario, **Paul Zuckerman**

Sponsors

NIDDK, DRC, NORC, GCRC, CCTS

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Thank you!

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