The Ketogenic Diet

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Background

- Published reports from **1920's** on Keto diet for epilepsy
- High-fat, low-protein, low-CHO diet
- **Classic KD**: 4:1:1 (fat : protein : CHO)
- **Modified Atkins (MAD)**: 1:1 (fat : protein and CHO)
  - CHO ~10-20g/day
- **Low glycemic index treatment (LGIT):** 40-60 g/d CHO w/ glycemic index < 50; 60% fat; 20-30% protein
- Also variants with **ketone esters**, **salts**, **MCT** (from coconut oil or palm kernel oil)

McDonald et al. Curr Opin Clin Nutr Metab Care 2019

Ketogenic Diets and Cancer

- Meta-analysis 11 studies, n=102, duration 2.4 – 134.7 wks
- Results
  - Inconclusive evidence on nutritional status, tumor effects, QoL
  - Diet adherence: **~49%**
  - **Adverse effects**: fatigue, constipation, diarrhea, vomiting, hyperuricemia

Sremanakova et al. J. Human Nutrition & Dietetics. 2019

Ketogenic Diets and Parkinson's disease

- Randomized, control trial; n=47; 8 wks
- Keto (<16g CHO) vs low-fat (<42g fat) CHO diet
- International Parkinson and Movement Disorder Society UPDRS (MDS-UPDRS) assessment by diet-blinded neurologist
- All participants continued L-dopa
- KD group had **greater improvement** in nonmotor sx
  - (i.e. mood disorders, cognitive changes, fatigue, sleep issues)

Phillips et al. Mov Disord. 2018

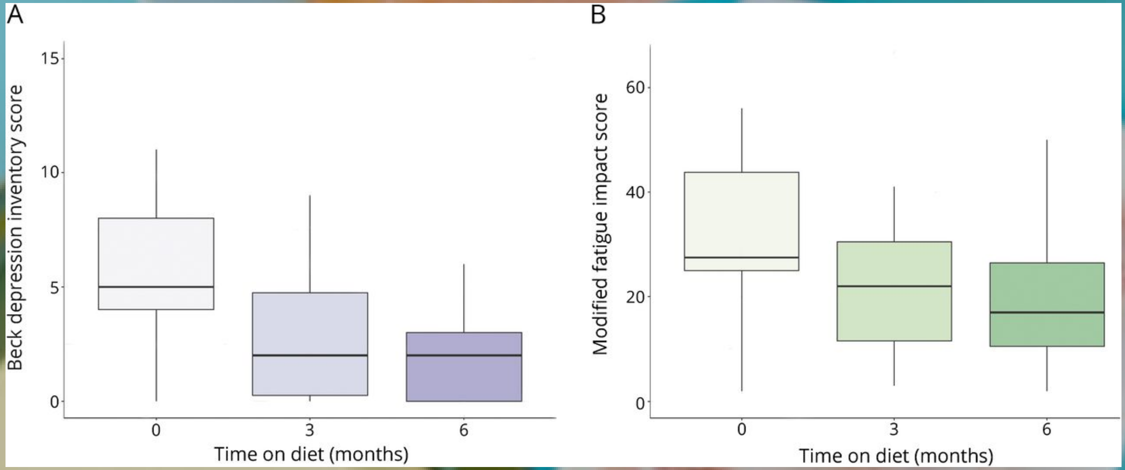
Ketogenic Diets and Epilepsy

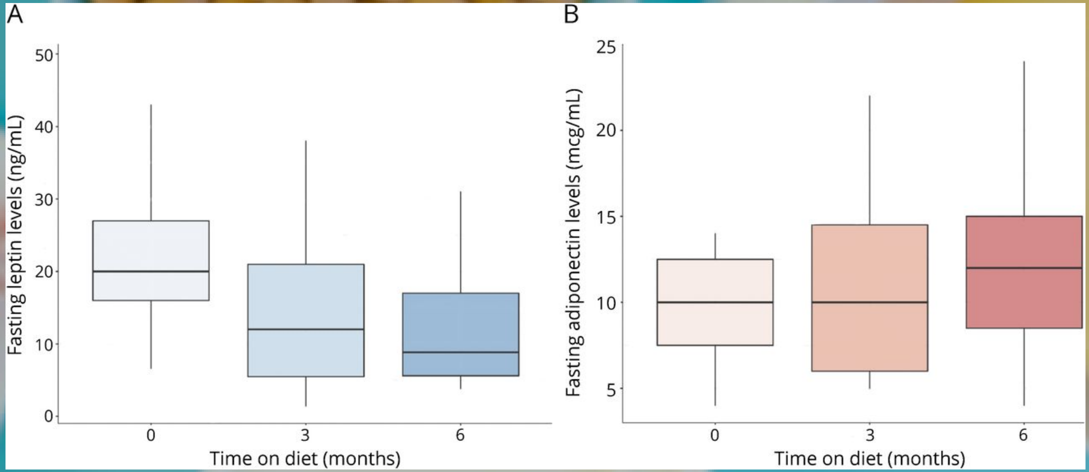
- Randomized clinical trial; n=75; age > 16 w/ ≥ 3 sz/month despite 3 antiepileptic drugs; duration 12 wks
- Modified Atkins Diet vs habitual diet
- Among completers (24 out of 37), >25% seizure reduction was **167%** ↑ (2.67; 95% CI 1.05-6.79)
- **35% dropout rate** in treatment arm
- Most common **side effects**: N/V, reflux, constipation and diarrhea

Kverneland et al. Epilepsia 2018

Ketogenic Diets and Multiple Sclerosis

- 6 mo, single-arm, open-label study; n = 20; urine ketone testing for adherence, MRI brain at baseline and 6 mos.
- Statistically significant reduction in **BMI** and **total fat mass** (p<0.0001), **fatigue** (p=0.002), **depression** (p=0.003), **leptin** (p< 0.0001)
- **75%** met adherence criteria

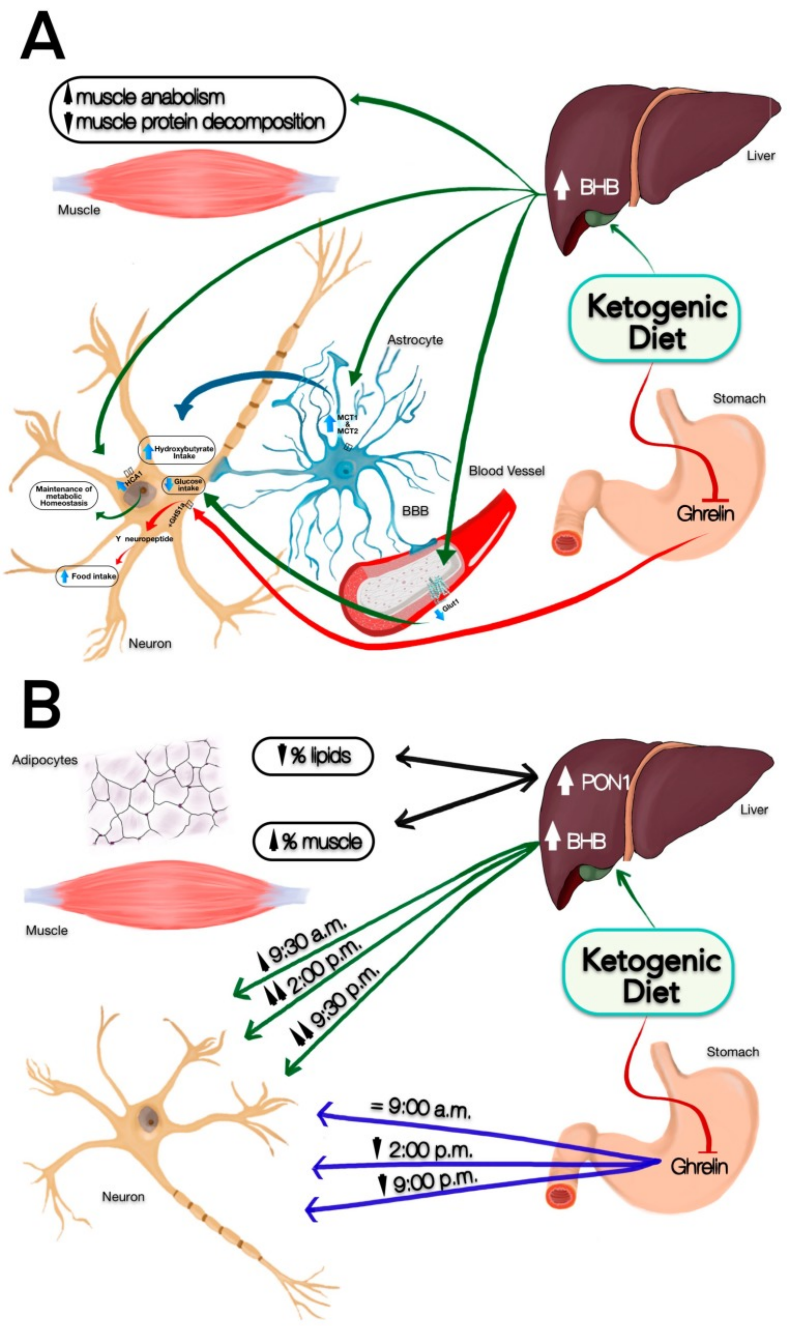




Brenton et al. Neurol Neuroimmunol Neuroinflamm. 2019

Ketogenic Diets and Multiple Sclerosis

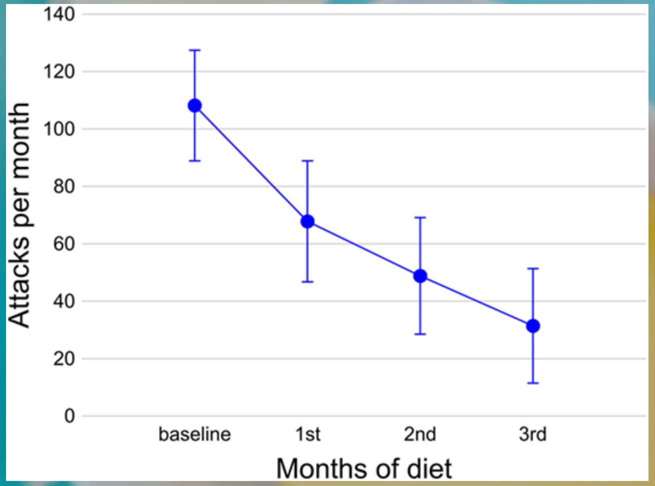
- Pilot study, 27 MS patients, hybrid Mediterranean ketogenic diet x 4months (20% protein, 40% CHO, 40% lipids; 60ml coconut oil daily)
- Significant ↑ in **muscle mass** (p=0.003), **BHB** (p=0.045), **satiety** (p=0.001), **PON1** (p=0.000)
- Significant ↓ in **fat mass** (p=0.000)
- PON1: paraoxonase
  - Oxidation marker, inhibits LDL oxidation
  - Prevents production of cytokines, inflammatory mediators, cell adhesion molecules



Benlloch et al. Nutrients. 2019

Ketogenic Diets and Cluster Headaches

- Prospective, **open-label**, **single-arm** clinical trial; n=18, 12-week Modified Atkins Diet (CHO 15g/d; protein 0.7-1.2g/kg/d), response defined as ≥ 50% attach reduction
- Cluster headache: unilateral trigeminovascular and autonomic system co-activation
  - HA persist weeks or months
  - If no remission then defined as chronic cluster headache (CCH)
- 11 pts experienced **full headache resolution**, 4 had **50% ↓ in monthly attacks**.
- Mean attacks went from 108.71 to 31.44 at 3rd month



Di Lorenzo et al. Frontiers in Neurol. 2018

Ketogenic Diets and Cluster Headaches

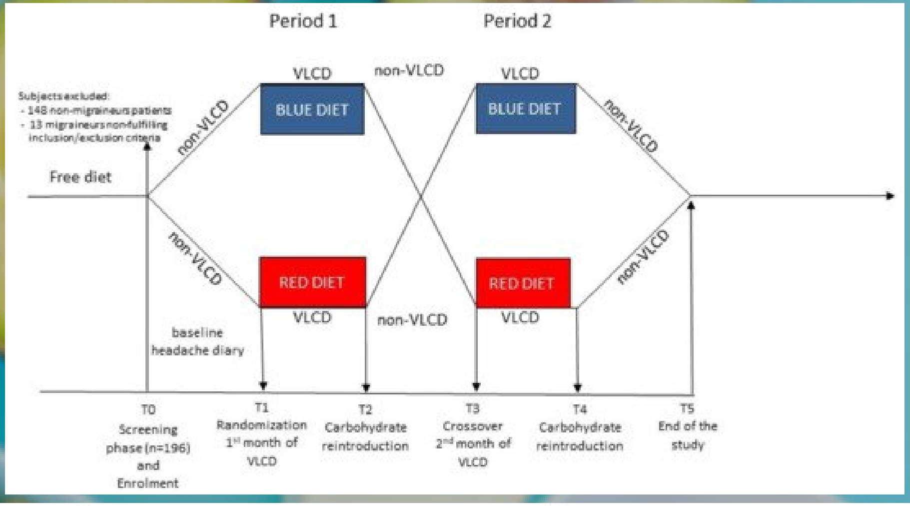
- Mechanims
  - KD ↑ brain DA activity (impaired in cluster headache)
  - Ketone bodies ↑ GABA activity.
    - GABA is protective in cluster headache and epilepsy

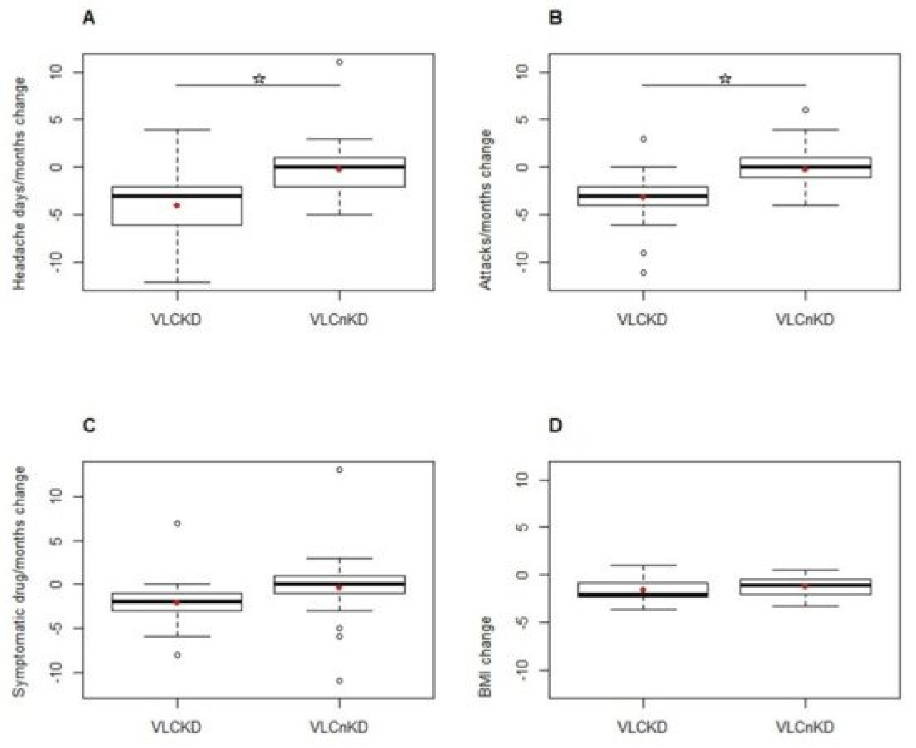
Di Lorenzo et al. Frontiers in Neurol. 2018

Ketogenic Diets and Migraines

- N =35 overweight/obese pts w/ migraines; randomized to very low calorie kegotenic (VLCKD) or normal (VLCnKD) x 1 month crossover.
- Migraine days
  - VLCKD: **-3.73 migraine days** vs VLCnKD ($p<0.0001$)
- 50% responder rate
  - VLCKD: **74.28%**
  - VLCnKD: 8.57%
- Migraine Attacks:
  - VLCKD: **-3.02** vs VLCnKD ($p<0.00001$)
- Weight loss **similar** between VLCKD and VLnCKD

Di Lorenzo et al. Nutrients. 2019

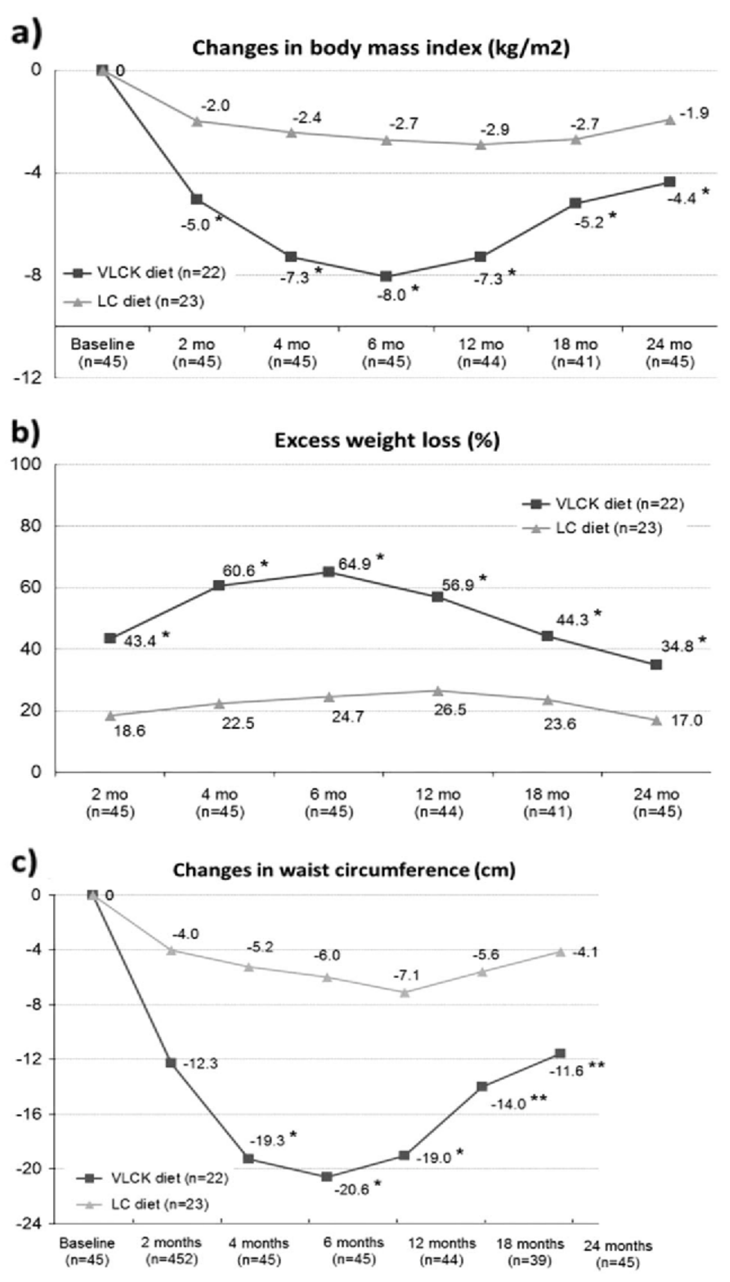




Ketogenic Diets and Weight loss

- 45 obese pts randomly assigned to VLCKD or standard low-calorie diet; **24 mo. f/u**

	VLCKD (600-800 kcal/d)	LCD (800-1500 kcal/d)	
Bodyweight	↓ 12.5 kg	↓ 4.4kg	P < 0.001
Waist Circumference	↓ 11.6cm	↓ 4.1cm	P < 0.001
Body Fat mass	↓ 8.8kg	↓ 3.8kg	P < 0.001
Visceral fat	↓ 600 g	↓ 202 g	P < 0.001



Ketogenic Diets and Weight loss

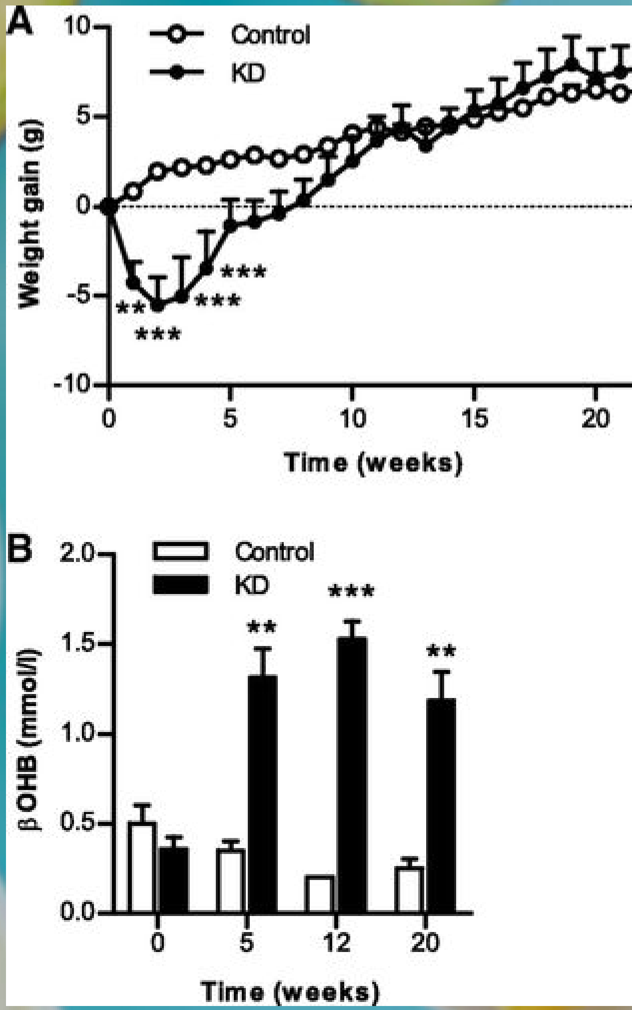
Study investigating glucose tolerance and α, β cell mass in KD fed mice.

Initial wt loss but **none** at 22 wks

Hepatic steatosis in KD mice at 22 week

Glucose intolerance w/ insufficient insulin sx from β cells.

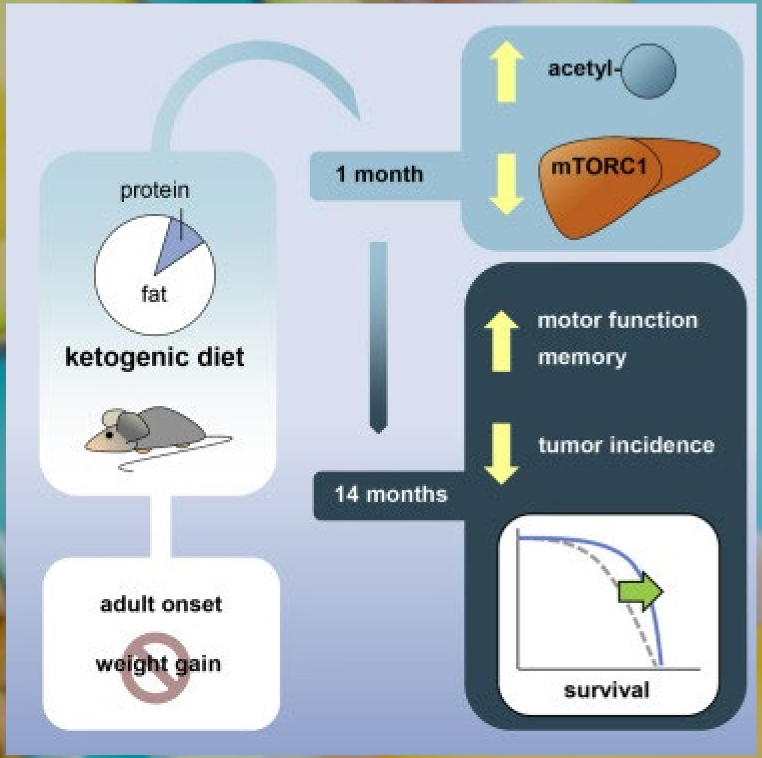
Both **β, α cell mass reduced** at 22 wks

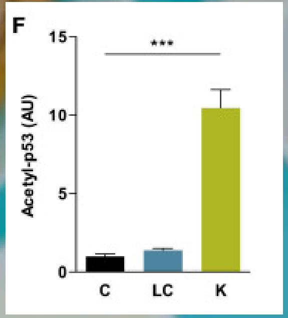


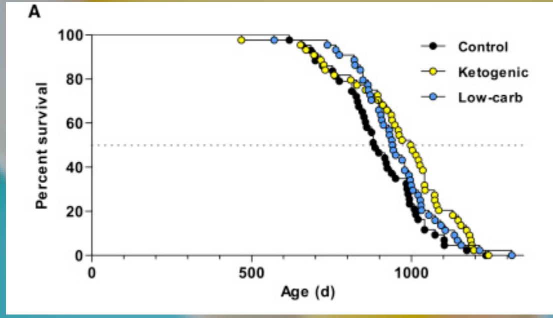
Ellenbroek et al. Am J Physiol Endocrinol Metab 2014

Ketogenic Diets and Lifespan

- Adult mice fed isocaloric control diet (65% kcal CHO), LCD (70% kcal fat), KD (89% kcal fat)
- **13.6% ↑ lifespan** in KD vs control
- **Tumor incidence (esp. histiocytic sarcoma) ↓** in KD vs control
- Acetylated p53 (tumor suppressor protein) **10x higher** in liver x 1 month on KD



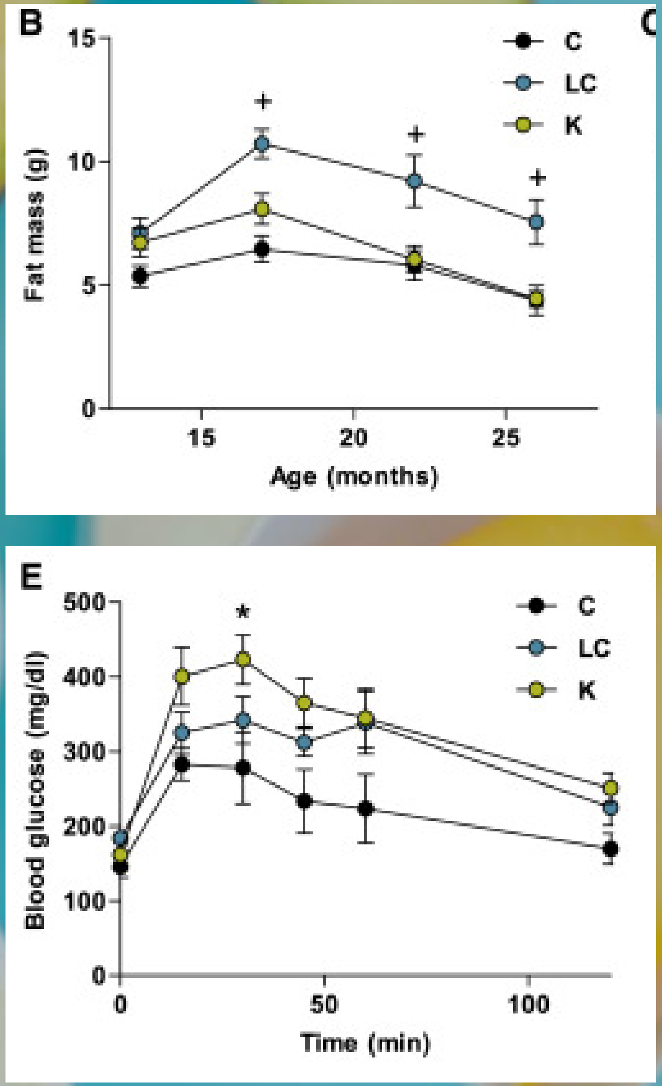




Roberts et al. Cell Metab. 2017

Ketogenic Diets and Metabolism

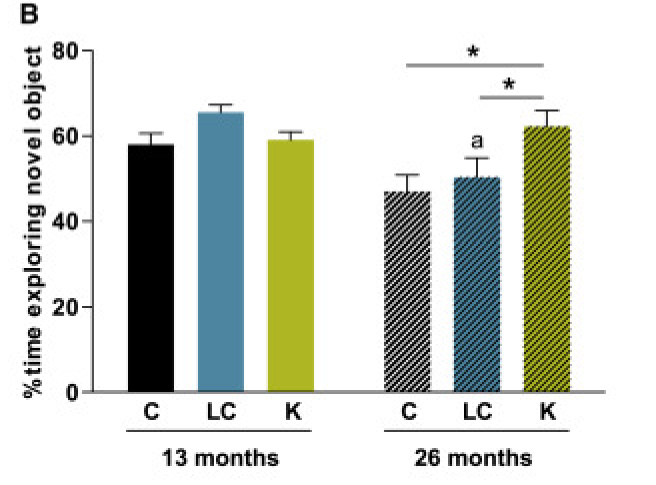
- Adult mice fed isocaloric control diet (65% kcal CHO), LCD (70% kcal fat), KD (89% kcal fat)
- LCD mice had **more fat mass** than control or ketogenic.
- Mice on KD had **impaired glucose tolerance**



Roberts et al. Cell Metab. 2017

Ketogenic Diets and Memory

- Adult mice fed isocaloric control diet (65% kcal CHO), LCD (70% kcal fat), KD (89% kcal fat)
- **Memory preserved** in old mice fed KD vs control tested via novel object recognition test



Roberts et al. Cell Metab. 2017

Ketogenic Diets and Metabolic Syndrome

10 men, 6 women, obese (BMI 39±8.3; age 41.3±10.7); randomized, crossover design to lo, med and hi CHO diet (eucaloric & isonitrogenous); duration = 16 wks

- Measured visceral adipose tissue and liver fat by MRI
- Measured lipoprotein particle subclass
- Starting mean hepatic fat **13.9%** (NAFLD)

Hyde et al. JCI Insight. 2019

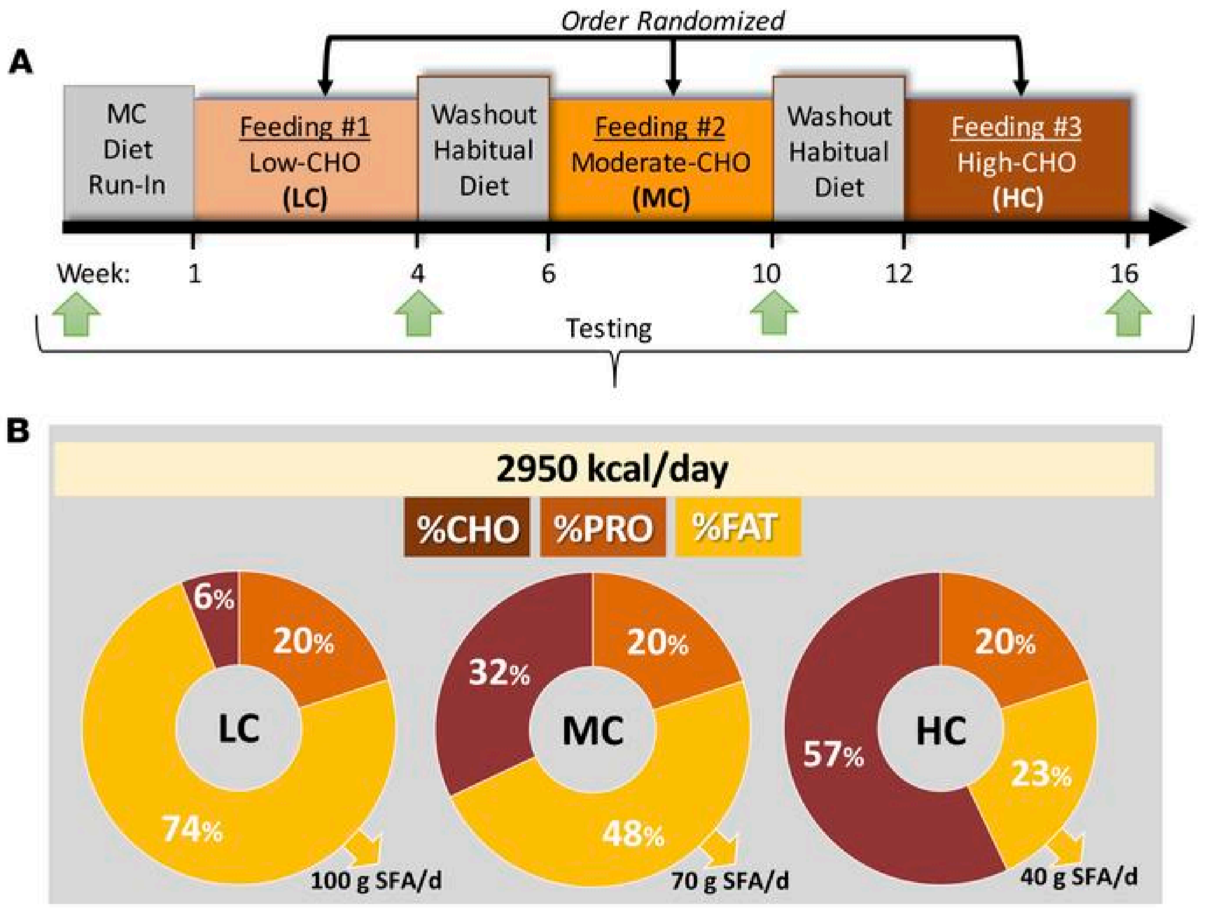


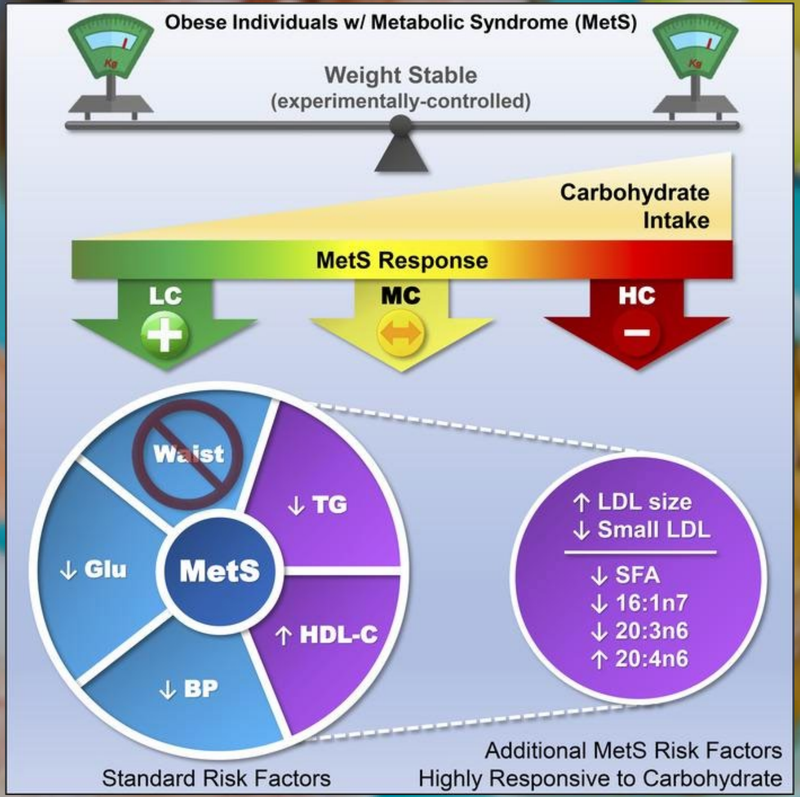
Table 1. Daily nutrient intake of controlled diets

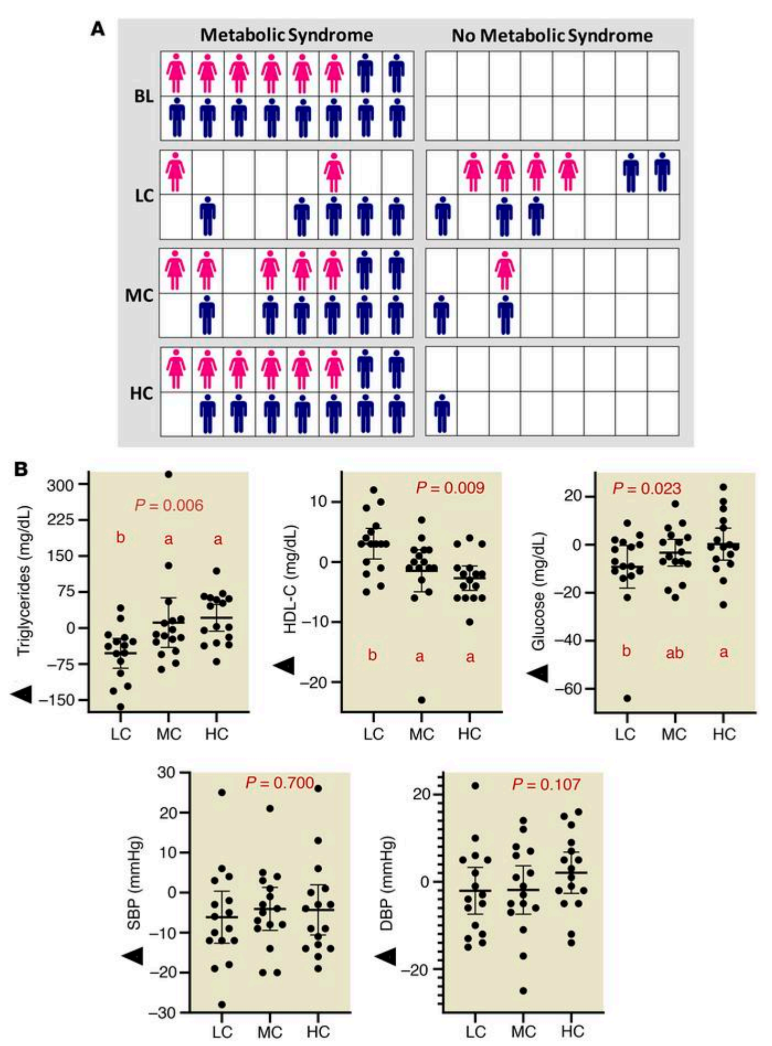
Nutrient	HC	MC	LC
Energy (kcal)		**2,950** (2035–3750)	
Protein (g)	**144** (100–184)	**146** (101–185)	**150** (103–190)
Carbohydrate (g)	**420** (290–534)	**234** (161–297)	**45** (31–58)
Fat (g)	**77** (53–97)	**159** (110–202)	**242** (167–307)
Saturated fat (g)	**40** (28–51)	**70** (48–89)	**100** (69–127)
Monounsaturated fat (g)	**21** (15–27)	**54** (37–69)	**86** (59–110)
Polyunsaturated fat (g)	**6** (5–8)	**21** (14–26)	**35** (24–45)
Cholesterol (mg)	**334** (231–425)	**503** (347–639)	**1,015** (701–1291)
Cheese (g)	**200** (138–255)	**201** (139–256)	**201** (139–256)
Calcium (mg)	**2,151** (1484–2734)	**2,229** (1537–2833)	**2,177** (1502–2768)
Fiber (g)	**25** (17–32)	**20** (14–25)	**14** (9–17)

Ketogenic Diets and Metabolic Syndrome

Results with LC:

- **Significantly lower resp exchange ratio (RER)** so ↑ fat oxidation (p,0.001)
- **Greater ↓ TG, ↑ HDL and lower glucose**
- **Decrease in circulating saturated fatty acids**
- **Significantly more phenotype A** (large buoyant LDL) than phenotype B (small, dense LDL)





Hyde et al. JCI Insight. 2019

Ketogenic Diets and Athletic Performance

14 intermediate to elite weight lifters; ages 34±10.5, n=5 female; random order, crossover design of usual ad libitum diet (>250g CHO) and LCKD ad libitum (<50g or ≤ 10% daily CHO intake); duration 3 months each phase

LCKD: ↓ 3.26kg weight and ↓ 2.26kg lean mass vs usual diet

No differences in lifting performances

TABLE 3. Primary and secondary study outcomes.*†

	Baseline	UD	LCKD
Body mass (kg)	77.9 (70.2–85.8)	79.4 (70.6–88.2)	76.0 (68.9–83.2)
Fat mass (kg)	13.7 (11.2–16.2)	14.7 (12.1–17.4)	13.7 (11.2–16.2)
Lean mass (kg)	61.1 (54.1–68.1)	61.5 (54.0–69.1)	59.3 (52.8–65.9)
1RM strength (kg)	132 (110–154)	137 (115–160)	135 (111–160)
RMR ($kJ \cdot d^{-1}$)	7,322 (5,983–8,665)	7,586 (6,485–8,673)	7,540 (6,360–8,715)
Measured RQ	0.79 (0.75–0.83)	0.77 (0.75–0.80)	0.76 (0.71–0.80)
Glucose ($mmol \cdot L^{-1}$)	4.9 (4.6–5.2)	5.1 (4.8–5.4)	4.9 (4.6–5.3)
Potassium ($mmol \cdot L^{-1}$)	4.3 (4.1–4.5)	4.4 (4.2–4.6)	4.7 (4.3–5.1)
Sodium ($mmol \cdot L^{-1}$)	145 (143.7–146.3)	143.9 (142.6–145.2)	145.1 (144.0–146.2)

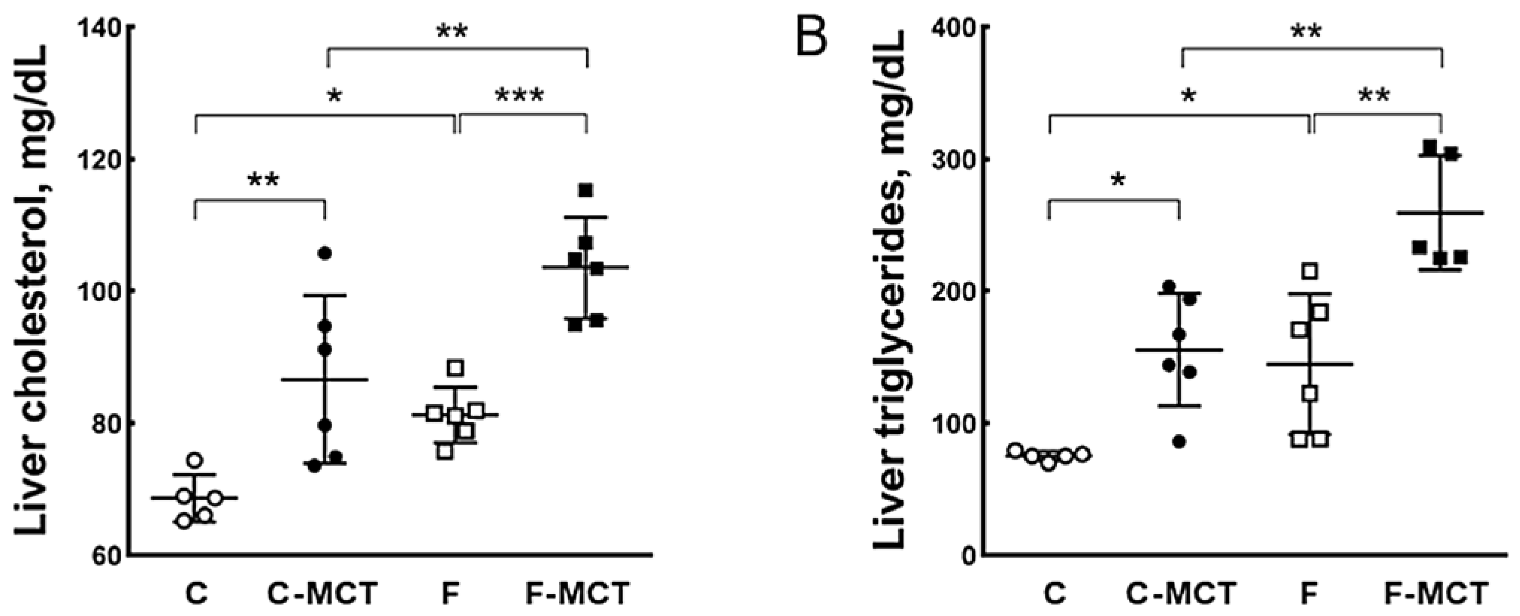
*UD = usual diet; LCKD = low-carbohydrate ketogenic diet; 1RM = 1 repetition maximum; RMR = resting metabolic rate; RQ = respiratory quotient; CI = confidence interval.
†Values are presented as mean (95% CI) for 12 participants.

Greene et al. J Strength Cond Res 2018

Ketogenic Diets and Body Composition

Medium Chain triglycerides (MCT) effect on high fructose diet provoked fatty liver

- 4 groups of mice: Control (C); C+MCT; fructose (f); F+MCT
- C-MCT showed **hepatic steatosis** and **inflammation**



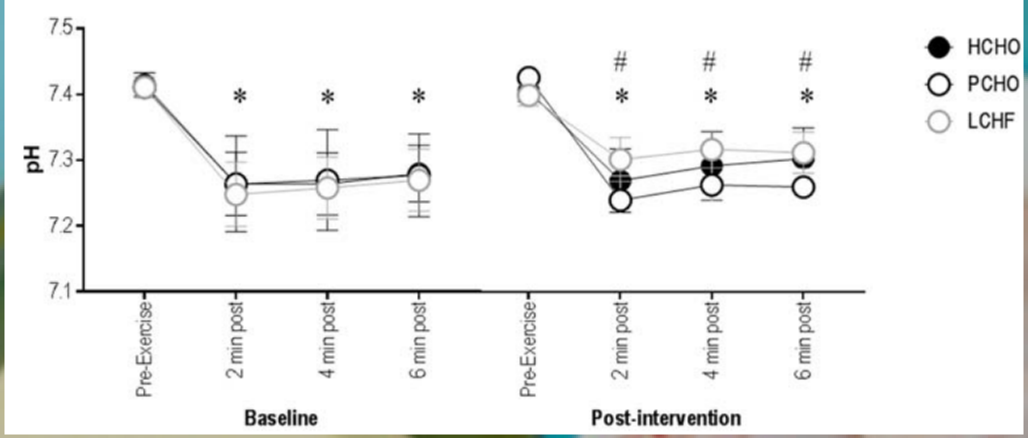
Guimaraes et al. Prostaglandins, Leukotrienes, Essential Fatty Acids. 2019

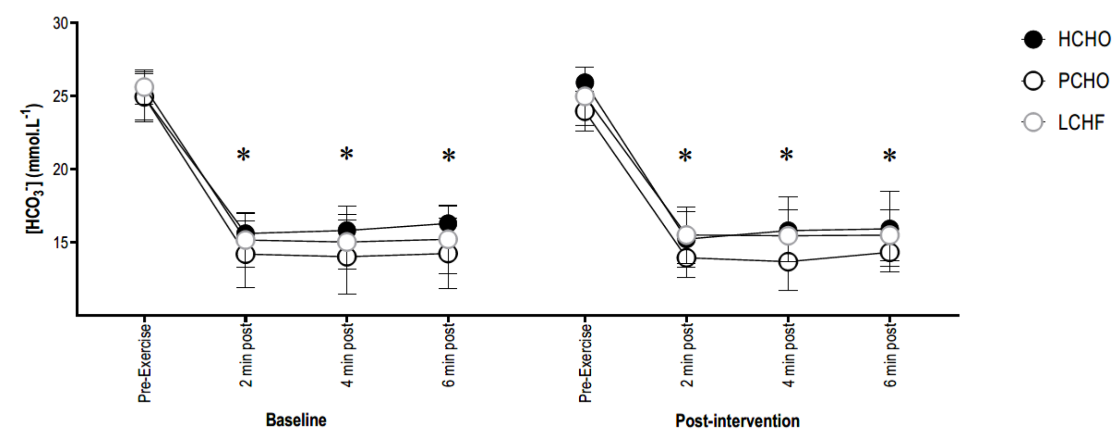
Ketogenic Diets and Acid/Base Balance

Non-randomized, parallel design; n=24 (17 M, 7 F) elite race walkers; duration 21 days of either LCHF, periodized CHO, or high CHO (control)

Net endogenous acid production **significantly higher** in LCHF

No significant difference in pH or HCO3 pre or post exercise for LCHF vs HCHO





Carr et al. Nutrients 2018

Ketogenic Diets and Cheat Days

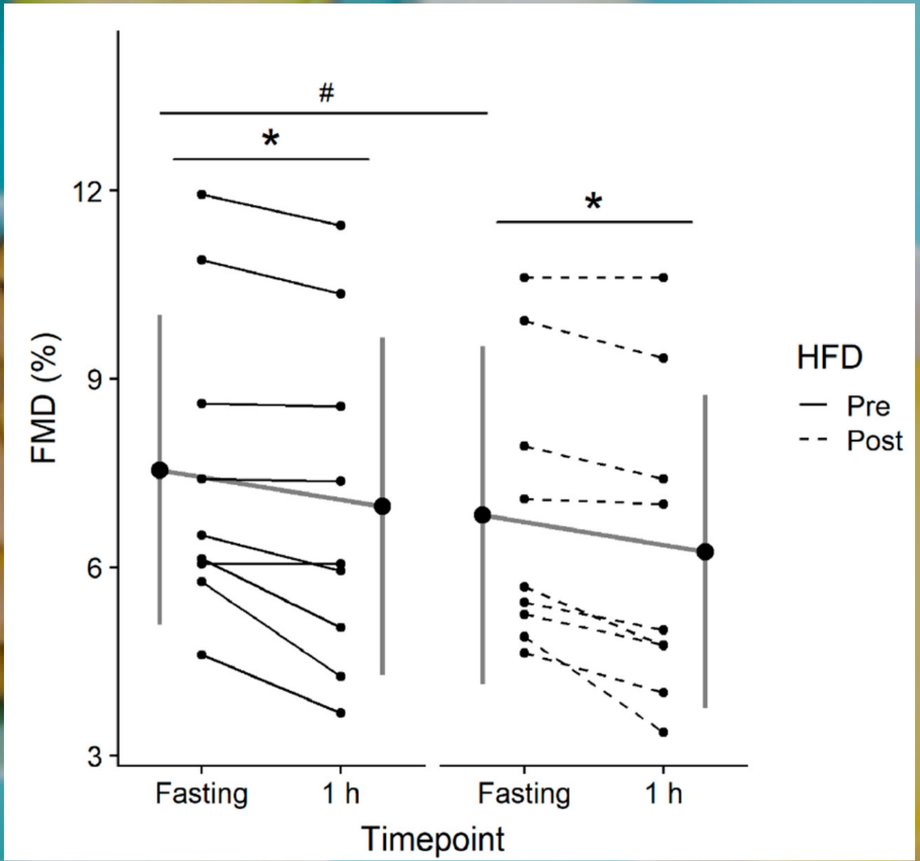
9 healthy males; bmi 23.2 ± 2 kg/m2; consumption of 75 gm glucose drink before & <24 hr after 7 day HFD (fat 70%; CHO 10%; Protein 20%)

- Measured **flow mediated dilation (FMD)** and **endothelial microparticles (EMP)** at 1, 2 hr post glucose consumption
- FMD: indicator of peripheral vascular function linked to CVD risk
- EMP: small vesicles shed from plasma membrane of endothelial cells 2/2 activation, apoptosis or damage. EMP proteins:
  - CD31+/CD42b: shed from apoptotic cells
  - CD62E+: inflammatory activation of endothelial cells

Durrer et al. Nutrients 2019

Ketogenic Diets and Cheat Days

- **Significant reduction** in FMD at fasting state post 7 days HFD.
- **Significant reduction** 1 hour post 75-g glucose drink consumption

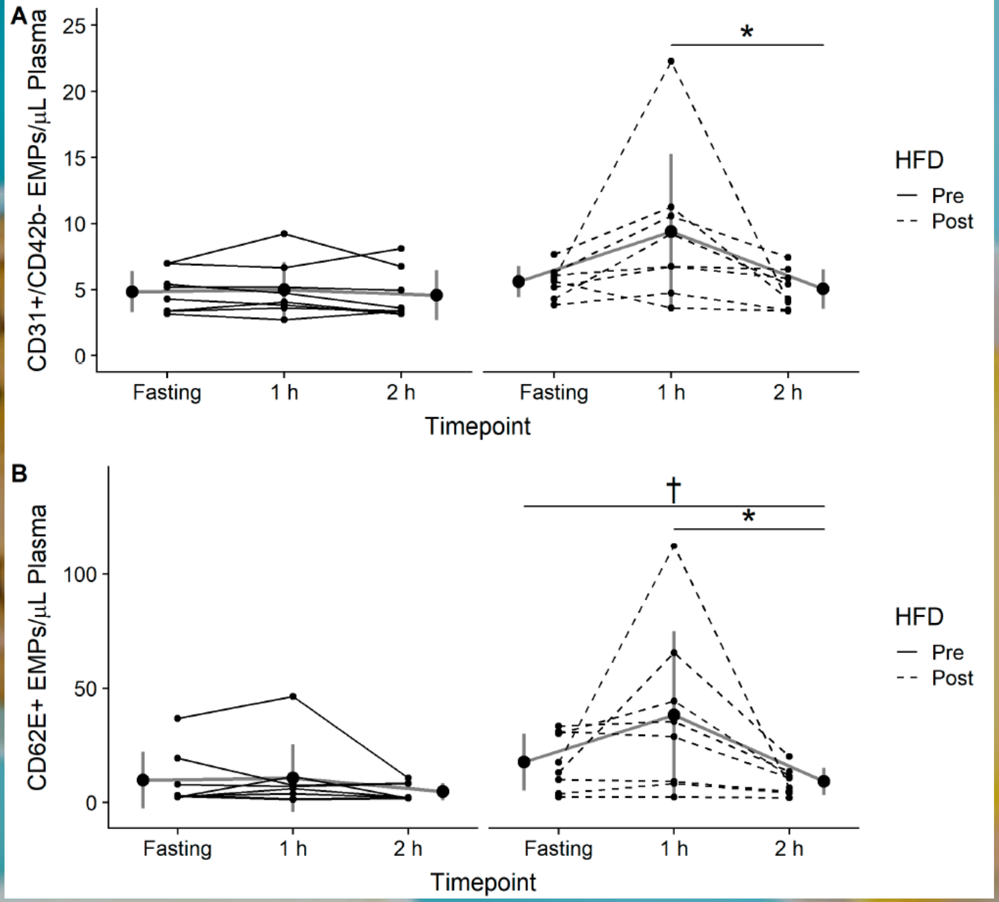


Durrer et al. Nutrients 2019

Ketogenic Diets and Cheat Days

Post 7 days HFD:

- CD31+/CD42b-EMP's **elevated** 1 hr and higher than fasting
- CD62E elevated at 1 hr and higher than fasting



Durrer et al. Nutrients 2019

Ketogenic Diets Side Effects and Concerns

- Missing out on fruits, vegetables, whole grains, legumes
  - All have strong link to lower all-cause, cancer and CVD mortality
- GI: N/V, diarrhea, constipation, GERD
- Dyslipidemia
- Atherosclerosis risk of KD
- Nutrient deficiencies (selenium deficiency in up to 50% of children on KD)
- Hyperuricemia, hypoproteinemia, hypomagnesemia, hyponatremia, metabolic acidosis.
- Growth failure: children on KDT are lower on weight and height.

www.uptodate.com; Accessed 10/14/19
www.mayoclinic.org; Accesed 10/14/19

Ketogenic Diets Side Effects and Concerns

- Carnitine deficiency (<20%)
- Risk for osteopenia and osteoporosis
- Kidney stones (as much as 7% of children)
- Once diet stopped, above adverse effects resolve. No late CVD, bone fractures or kidney stones after stopping diet
- Difficult to sustain
- Data on Plant based keto lacking
- Few long term studies

www.uptodate.com; Accessed 10/14/19
www.mayoclinic.org; Accesed 10/14/19

Bottom Line

- Ketogenic diet can produce beneficial metabolic and neurologic effects in the short term.
- Long term effects unknown
- Also unknown are effects during pregnancy, breastfeeding, childhood/adolescent years, cancer

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KAISER PERMANENTE.

Thank You

for joining today's session

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