Ketogenic Diet Literature Review

by Sarah Ballantyne, PhD and Denise Minger

This is a literature review of the range of health conditions ketogenic diets have been investigated for, encompassing the documented benefits, lack of advantage, adverse effects, and mechanisms. Also included is a selection of papers pertaining to the ketogenic diet and the Inuit Eskimos. This document does not contain commentary, but only summaries of research reports and links to original publications. However, this document does include the full spectrum of ketogenic diet studies, including those reporting serious health detriment, in order to demonstrate that the literature does not ubiquitously support ketogenic diets and that health risk is inherent with this therapeutic strategy.

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Sarah Ballantyne, PhD

Sarah Ballantyne, Ph.D. is the creator of the award-winning online resource www.ThePaleoMom.com; cohost of the syndicated top-rated The Paleo View Podcast; and *New York Times* bestselling author of *The Paleo Approach* and *The Paleo Approach Cookbook*. Sarah earned her doctorate degree in medical biophysics at the age of 26 and spent the next four years doing research on innate immunity, gene therapy and cell biology, earning a variety of awards for research excellence along the way. Sarah's transition from academic researcher to stay-at-home mom to award-winning and internationally-recognized health advocate and educator was motivated by her own health journey, which included losing 120 pounds and using both diet and lifestyle to mitigate and reverse a dozen diagnosed health conditions. Her passion for scientific literacy and her talent for distilling scientific concepts into straightforward and accessible explanations form the foundation of her work and her dedication to improving public health.

Denise Minger

Denise Minger is a health author, blogger, and public speaker with a reputation for aggressively challenging today's leading voices of conventional wisdom. Her meticulously researched critiques and presentations have made her a major player in the progressive health community, and a major thorn in the side of both mainstream nutritionists other health figures promoting flawed dietary dogma. She runs a blog at http://www.rawfoodsos.com and published her first book, "Death by Food Pyramid," in 2014.

Benefits

(Click name for description of study and outcomes)

Epilepsy seizure reduction in children

- Kinsman, et al., 1992
- Vining, et al., 1998
- Pulsifer, et al., 2001
- Nordli, et al., 2001

Epilepsy seizure reduction in adults

- Barborka, 1928
- Sirven, et al., 1999

Epilepsy seizure reduction even after discontinuing diet

- Marsh, et al., 2006

PCOS

- Mavropoulos, et al., 2005

Cognitive and behavioral improvements (non-Autism)

- Kinsman, et al., 1992
- Pulsifer, et al., 2001
- Nordli, et al., 2001
- Krikorian, et al., 2010

Autism improvements

- Evangeliou, et al., 2003

Neurodegenerative disorder improvements (Alzheimer's, Parkinson's)

- Gasior, et al., 2006

Traumatic brain injury protection

- Hu, et al., 2009

Improved bipolar symptoms

- El-Mallakh and Paskitti, 2001
- Phelps, et al., 2013

Appetite suppression

- Sumithran, et al., 2013

Increased fat mass loss

- Dashti, et al., 2004
- Krikorian, et al., 2010

- Paoli, et al., 2011
- Saslow, et al., 2014

Decreased tumor size
- Nebeling, et al., 1995
- Allen, et al., 2013b

Athletic performance
- Rhyu, et al., 2014

Improved glycemic control or diabetes
- Yancy, et al., 2005
- Saslow, et al., 2014

Improved blood lipids
- Sharman, et al., 2002
- Dashti, et al., 2004
- Yancy, et al., 2004
- Paoli, et al., 2011

Studies in chronological order:

Barborka, 1928: "Ketogenic Diet Treatment of Epilepsy in Adults"

Duration: Between 3 months and 3 years
Population: 32 patients aged 17 to 42
Benefit:
- 7 patients controlled their epilepsy
- 7 patients saw definite benefit (seizure reduction)
- 2 patients saw control of grand mal (but not petit mal) seizures
- 13 patients saw no benefit (9 may have been due to improper implementation of the diet)

Kinsman, et al., 1992: "Efficacy of the ketogenic diet for intractable seizure disorders: review of 58 cases"

Population: 58 epilepsy patients
Benefit:
- 36% of patients became more alert
- 23% had improved behavior
- 64% reduced antiepileptic medications

Nebeling, et al., 1995: "Effects of a ketogenic diet on tumor metabolism and nutritional status in pediatric oncology patients: two case reports"

Duration: 8 weeks
Population: 2 female pediatric patients with advanced stage malignant Astrocytoma tumors
Benefit:

- 21.8% average decrease in glucose uptake at the tumor site in both females
- One patient exhibited significant clinical improvements in mood and new skill development while on diet

Vining, et al., 1998: "A multicenter study of the efficacy of the ketogenic diet"

Duration: Up to 1 year
Population: 51 epileptic children
Benefit:

- After 6 months, 28 (55%) had at least a 50% decrease from baseline
- At 1 year, 40% of those starting the diet had a greater than 50% decrease in seizures
- 5 patients (10%) free of seizures at 1 year

Table 2. Outcomes of the Ketogenic Diet*

Initiated Diet	3 mo	6 mo	12 mo
No. on diet	45 (88)	35 (69)	24 (47)
>90% Control of seizures†	13 (25)	15 (29)	11 (22)
50%-90% Control of seizures	15 (29)	12 (24)	9 (18)
<50% Control of seizures	17 (33)	8 (16)	4 (8)
Discontinued diet	6 (12)	14 (27)	23 (45)
Lost to follow-up	0	2	4

**N = 51. Values are number (percentage).*
†Number free of seizures were the following: 6 (3 months), 6 (6 months), and 5 (12 months).

Sirven, et al., 1999: "The ketogenic diet for intractable epilepsy in adults: preliminary results"

Duration: 8+ months
Population: 11 adults (9 women, 2 men) ages 19 – 45 years

Benefit:

- At 8 months, 3 patients had 50 – 70% decrease in seizure frequency
- 1 patient had less than 50% seizure decrease
- 4 patients had discontinued diet: 2 due to no appreciable change in seizure, 2 due to inability to maintain ketosis at home

El-Mallakh and Paskitti, 2001: "The ketogenic diet may have mood-stabilizing properties"

Theoretical Paper
Mechanism: "the extracellular changes that occur in ketosis would be expected to decrease intracellular sodium concentrations, a common property of all effective mood stabilizers"

Pulsifer, et al., 2001: "Effects of ketogenic diet on development and behavior: preliminary report of a prospective study"

Duration: 8 – 18 months follow-up
Population: 34 children (out of original group of 65), 18 months - 14.5 years
Benefit:

- Seizure frequency reduced on average from 25 seizures a day at baseline to 1.8 seizures per day at follow-up
- 30 out of 34 patients saw reduced seizure frequency; 10 were completely seizure free
- Significant improvement in developmental quotient, attention, and social function

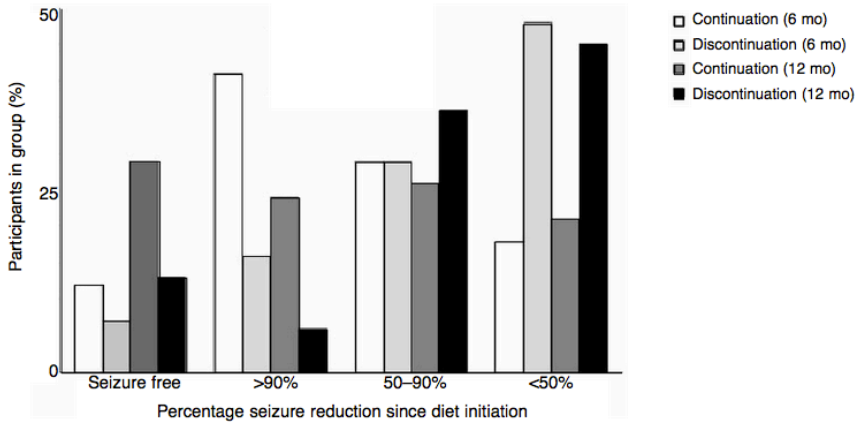


Figure 1: *Seizure reduction by 6- and 12-month follow-up for diet continuation group (n=34) and discontinuation group (n=31). Difference between groups was significant (p<0.05).*

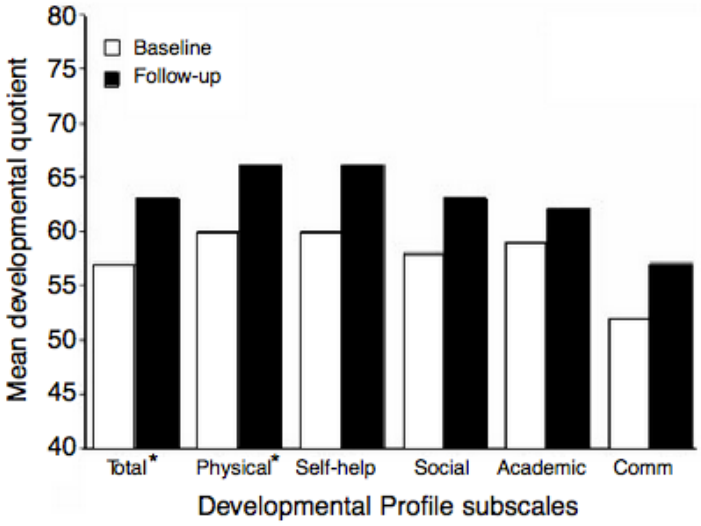


Figure 2: *Developmental Profile-II developmental quotient at baseline (before diet) and follow-up (n=34). Comm, communication. *Significant difference (p<0.05).*

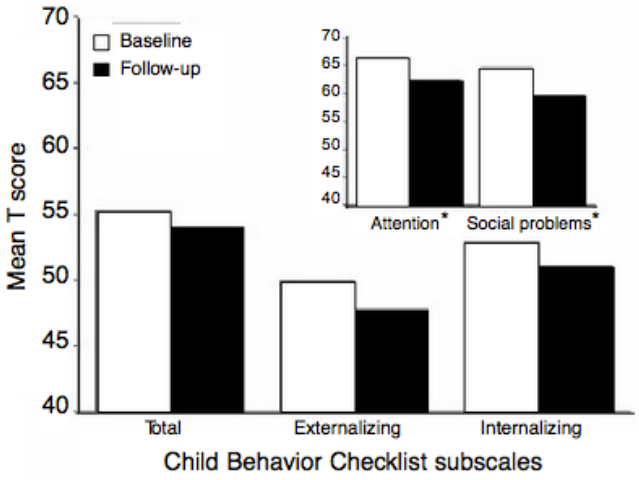


Figure 3: *Child Behavior Checklist mean scores at baseline (before diet) and follow-up (n=34). *Significant difference (p<0.05).*

Nordli, et al., 2001: "Experience with ketogenic diet in infants"

Population: 32 infants
Benefit:

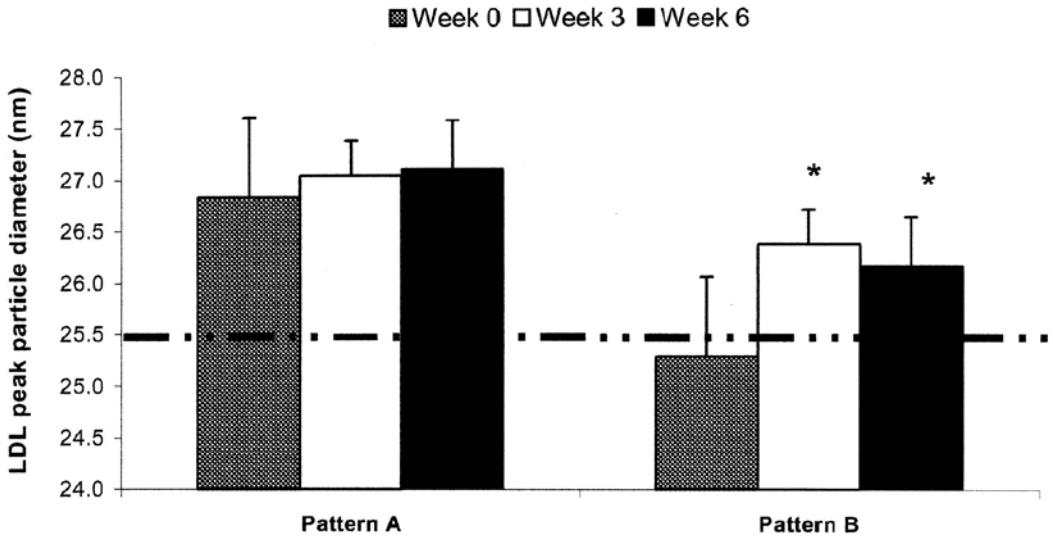
- 19.4% became seizure free
- 35.5% had over 50% reduction in seizure frequency

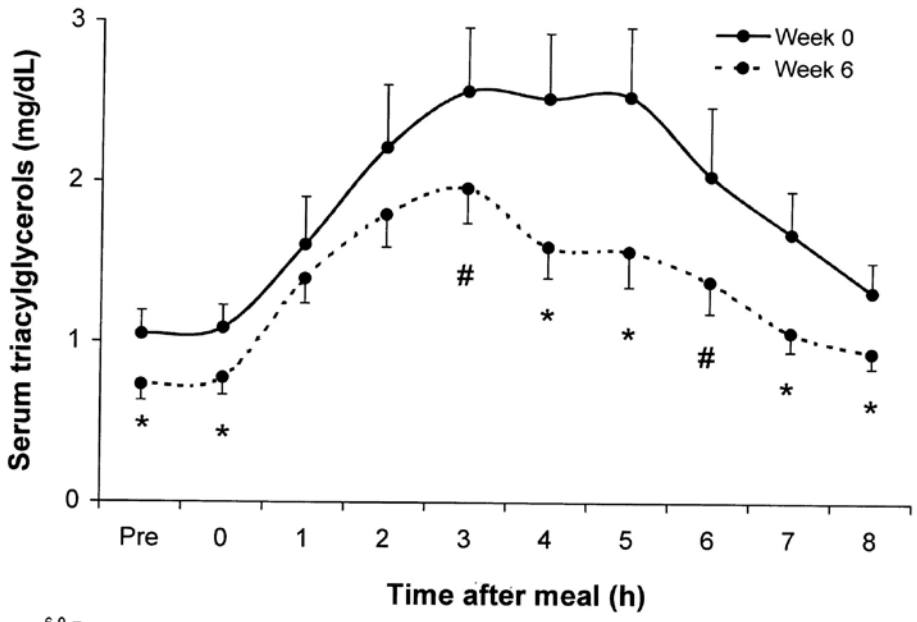
- Improvements in behavior and function, alertness, activity level, and socialization

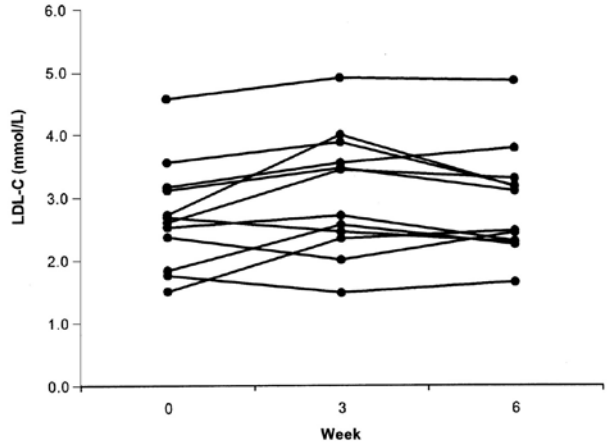
Sharman, et al., 2002: "A Ketogenic Diet Favorably Affects Serum Biomarkers for Cardiovascular Disease in Normal-Weight Men"

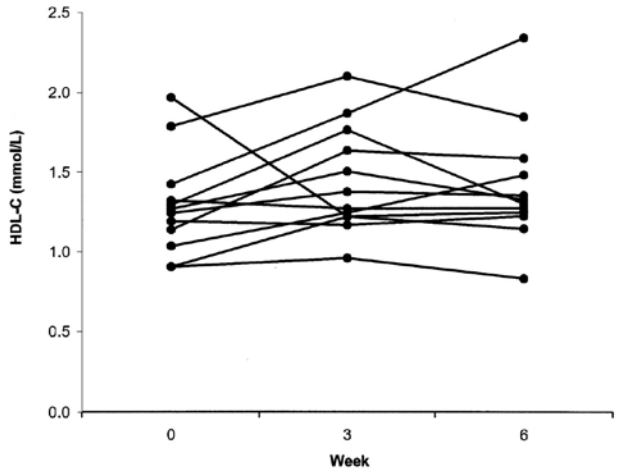
Duration: 6 weeks
Population: 20 normal weight men with normal blood lipids; 12 eating ketogenic diet (30% protein, 8% carbohydrate and 61% fat) and 8 eating their normal diet (17% protein, 47% carbohydrate and 32% fat)
Benefit:

- Men with LDL pattern B increased mean and peak LDL particle diameter (moving towards pattern A)
- Significant decreases in fasting triglycerides (-33%)
- Decreased postprandial lipemia after fat-rich meal (-29%)
- Decreased fasting insulin (-34%)
- *Variable responses:*
    - Total cholesterol decreased in 5 people (range: -2% to -17%) and increased in 7 (range: 1% to 60%)
    - LDL decreased in 4 people and increased in 7
    - HDL decreased in 3 people (range: -6% to -20%) and increased in 9 (range: 1% to 71%)
    - Fasting triglycerides increased in 1 person




Serum triacylglycerols (mg/dL)
Week 0
Week 6
Pre
0
1
2
3
4
5
6
7
8
Time after meal (h)


LDL-C (mmol/L)
Week


HDL-C (mmol/L)
Week

Evangeliou, et al., 2003: "Application of a ketogenic diet in children with autistic behavior: pilot study"

Duration: 6 months
Population: 30 autistic children aged 4 to 10
Benefit:

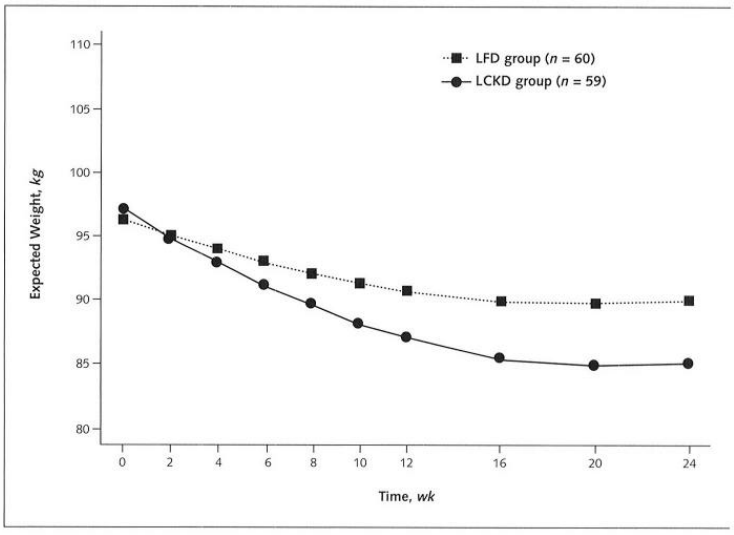
- 60% saw improvement in several parameters and in accordance with the Childhood Autism Rating Scale
- 2 patients saw significant improvement (>12 units of the Childhood Autism Rating Scale)
- 8 patients saw average improvement (>8-12 units)
- 8 patients saw minor improvement (2-8 units)

Yancy, et al., 2004: "A Low-Carbohydrate, Ketogenic Diet versus a Low-Fat Diet To Treat Obesity and Hyperlipidemia: A Randomized, Controlled Trial"

Duration: 24 weeks
Population: 120 overweight, hyperlipidemic adults placed on either ketogenic or low-fat, low-cholesterol diet
Benefit:

- Compared to low-fat group, ketogenic group experienced greater weight loss
- Ketogenic group experienced lower average triglycerides
- Ketogenic group experienced higher average HDL
- No difference in LDL between groups

Figure 2. Expected mean body weight over time, by diet group.



Expected mean body weight determined by linear mixed-effects model analysis. $P < 0.001$ for linear and quadratic time-by-diet group interaction terms. LCKD = low-carbohydrate, ketogenic diet; LFD = low-fat, low-cholesterol, reduced-calorie diet.

Table 2. Effect of Diet Programs on Fasting Lipid Profiles*

Variable	Low-Fat Diet Group (n = 60)				Low-Carbohydrate, Ketogenic Diet Group (n = 59)				*P* Value for Between-Group Comparison
	Week 0	Week 24	Change	*P* Value	Week 0	Week 24	Change	*P* Value	
Total cholesterol level, *mmol/L (mg/dL)*	6.20 (239.9)	5.85 (226.2)	−0.35 (−13.7)	0.008	6.32 (244.5)	6.11 (236.4)	−0.21 (−8.1)	0.08	>0.2
Triglyceride level, *mmol/L (mg/dL)*	2.15 (190.7)	1.84 (162.7)	−0.31 (−27.9)	0.02	1.78 (157.8)	0.94 (83.6)	−0.84 (−74.2)	<0.001	0.004
LDL cholesterol level, *mmol/L (mg/dL)*	3.83 (148.0)	3.64 (140.6)	−0.19 (−7.4)	0.2	4.07 (157.2)	4.11 (158.8)	0.04 (1.6)	>0.2	0.2
HDL cholesterol level, *mmol/L (mg/dL)*	1.40 (54.1)	1.36 (52.5)	−0.04 (−1.6)	>0.2	1.43 (55.4)	1.57 (60.9)	0.14 (5.5)	<0.001	<0.001
Ratio of total cholesterol to HDL cholesterol	4.7	4.4	−0.3	0.09	4.7	4.1	−0.6	<0.001	0.09
Ratio of triglyceride to HDL cholesterol	4.1	3.4	−0.6	0.02	3.2	1.6	−1.6	<0.001	0.02

* Values are expected means by linear mixed-effects model analysis. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Dashti, et al., 2004: "Long-term effects of a ketogenic diet in obese patients"

Duration: 24 weeks
Population: 83 obese patients eating ketogenic diet (30g carbohydrate; fat content 20% saturated and 80% unsaturated)
Benefit:

- Bodyweight and BMI significantly decreased
- Total cholesterol, LDL, and triglycerides significantly decreased
- HDL significantly increased
- Blood sugar significantly decreased

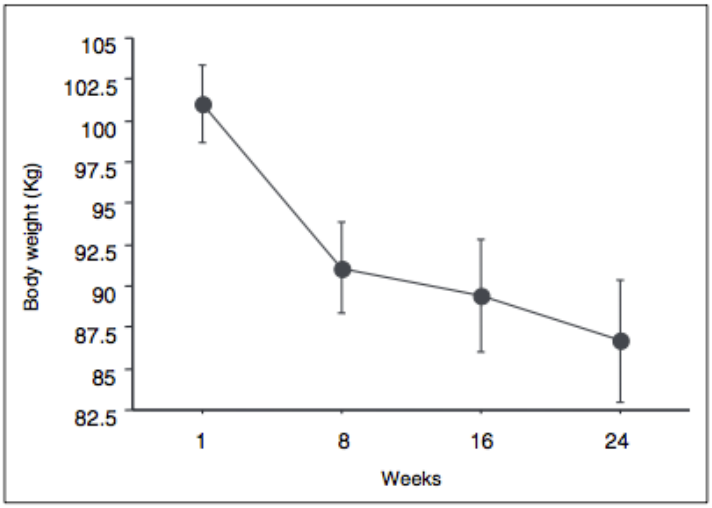


Figure 1) *Reduction in body weight at eight, 16 and 24 weeks following the administration of the ketogenic diet in obese patients. The weights are expressed as mean ± SEM*

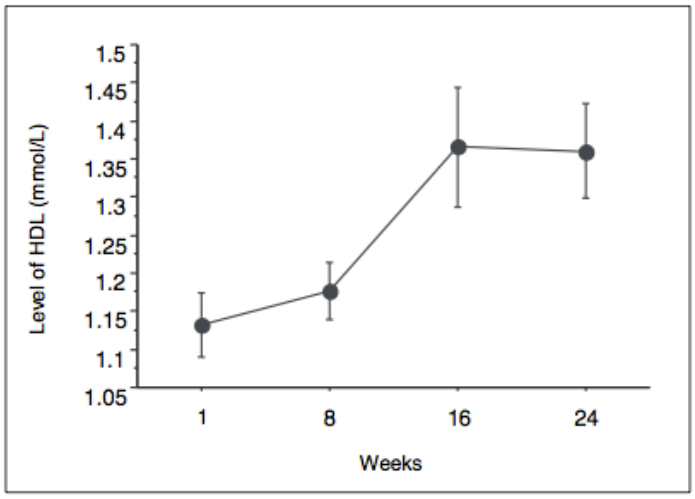


Figure 4) *Changes in the level of high density lipoprotein (HDL) cholesterol in obese patients during treatment with a ketogenic diet for a period of 24 weeks. Data are expressed as mean ± SEM*

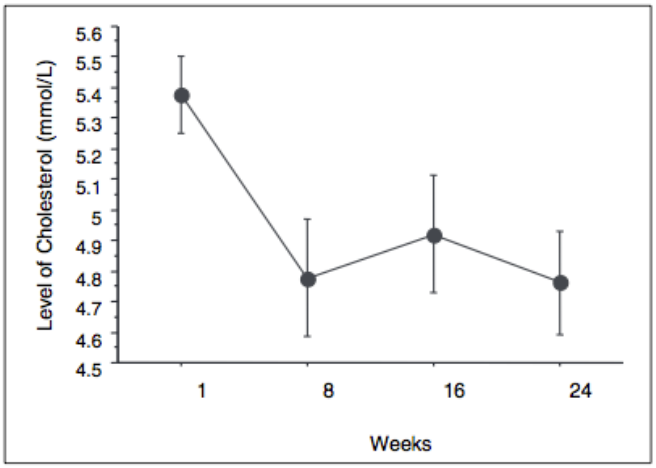


Figure 3) *Decreased levels of total cholesterol (expressed as mean ± SEM) in obese patients at eight, 16 and 24 weeks during the administration of a ketogenic diet*

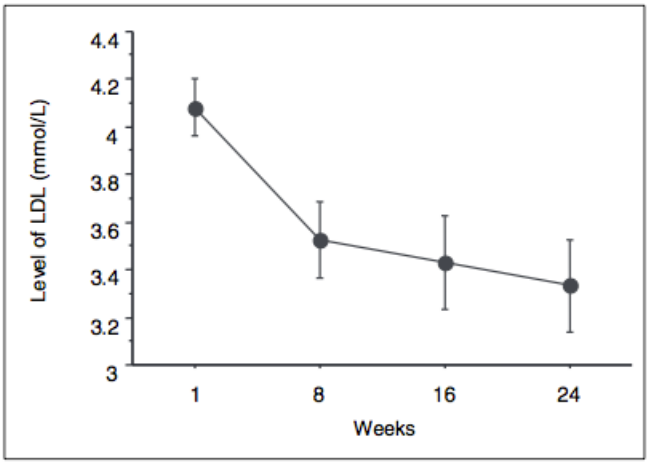


Figure 5) *Changes in the level of low density lipoprotein (LDL) cholesterol during treatment with a ketogenic diet in obese patients at eight, 16 and 24 weeks. The values are expressed as mean ± SEM*

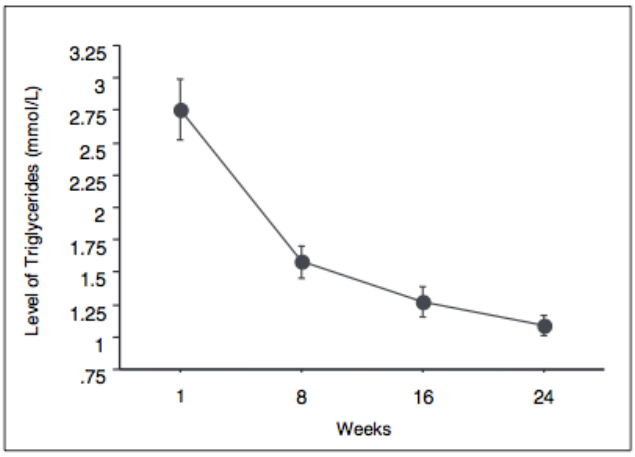


Figure 6) *Changes in the level of triglycerides in obese patients during treatment with a ketogenic diet over a period of 24 weeks. The values are expressed as mean ± SEM*

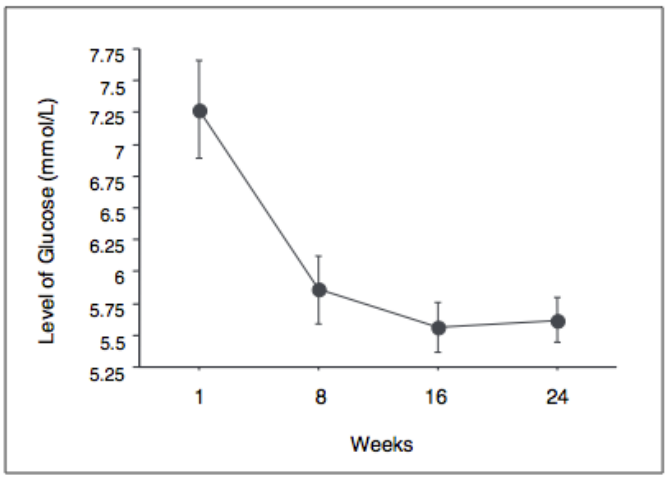


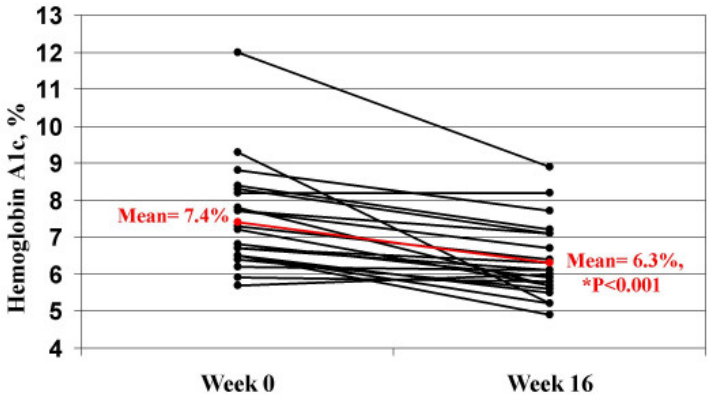
Figure 7) *Decreased levels of blood glucose (expressed as mean ± SEM) in obese patients at eight, 16 and 24 weeks during the administration of a ketogenic diet*

Yancy, et al., 2005: "A low-carbohydrate, ketogenic diet to treat type 2 diabetes"

Duration: 16 weeks
Population: 21 overweight adults with type 2 diabetes; 35 – 75 years old
Benefit:

- Diabetes medications discontinued in 7 people and reduced in 10; unchanged in 4
- Average body wewight decreased by 6.6%
- Fasting triglycerides decreased 42%

- Hemoglobin A1c decreased from 7.5% at baseline to 6.3% at week 16, a 1.2% absolute decrease and a 16% relative decrease



***Hemoglobin A1c for each participant**. *Red line is the group mean. P value is for the mean change from baseline.*

[Mavropoulos, et al., 2005: "The effects of a low-carbohydrate, ketogenic diet on polycystic ovary syndrome: A pilot study"]

Duration: 24 weeks
Population: 11 women with PCOS
Benefit:

- Significant reductions in body weight (-12%)
- Significant reductions in free testosterone (-22%)
- Significant reductions in LH/FSH ratio (-36%)
- Significant reductions in fasting insulin (-54%)
- Two pregnancies despite previous infertility problems

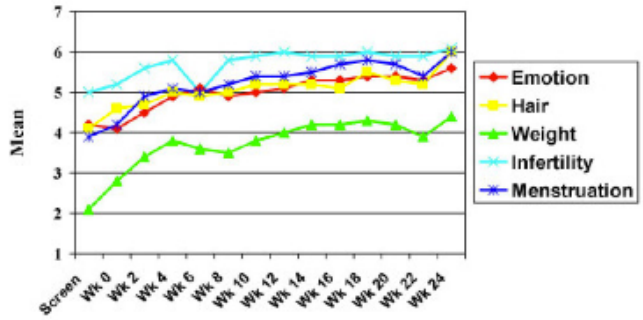


Figure 1
Effect of Diet on PCOS-Q Scores. The effect of a low-carbohydrate, ketogenic diet program on the mean poly-cystic ovary syndrome specific questionnaire (PCOS-Q) domain scores is shown over a 24 week period

Gasior, et al., 2006: "Neuroprotective and disease-modifying effects of the ketogenic diet"

Review and Theoretical Paper
Benefit: "Although the mechanisms are not yet well defined, it is plausible that neuroprotection results from enhanced neuronal energy reserves, which improve the ability of neurons to resist metabolic challenges, and possibly through other actions including antioxidant and anti-inflammatory effects."

Marsh, et al., 2006: "The outcome of children with intractable seizures: a 3- to 6-year follow-up of 67 children who remained on the ketogenic diet less than one year"

Duration: Up to 1 year on diet and 3 to 6 years follow-up
Population: 151 children
Benefit:

- Almost half of children who discontinued diet during first year had decrease in seizures when assessed 3-6 years later
- 22% of the above became seizure-free without surgery

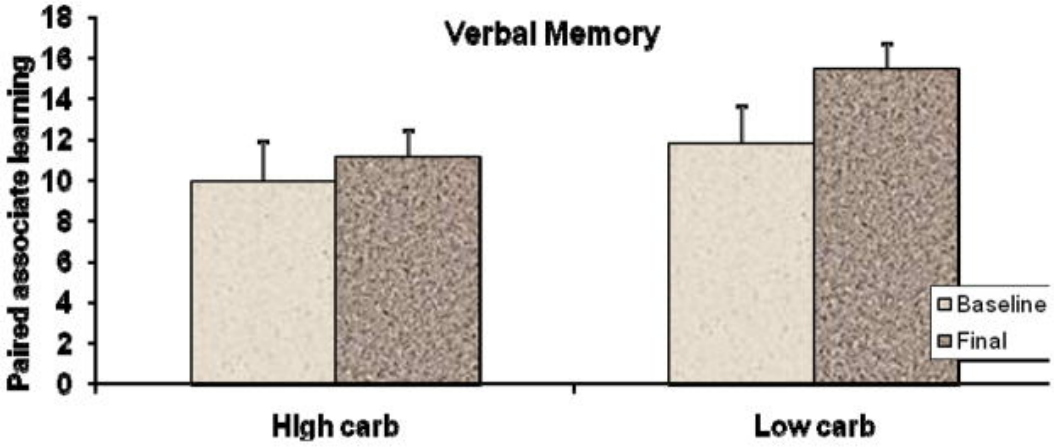
Hu, et al., 2009: "The protective effect of the ketogenic diet on traumatic brain injury-induced cell death in juvenile rats"

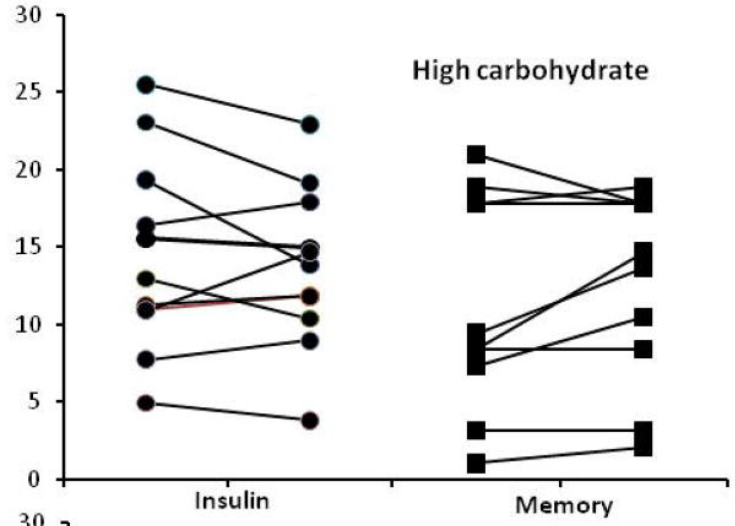
Animal Model
Benefit: "The results indicated that both Bax mRNA and protein levels were significantly elevated 72 hours after [traumatic brain injury] and decreased by KD administration. Neither [traumatic brain injury] nor the KD affected Bcl-2 mRNA and protein levels. KD administration also reduced brain oedema and cellular apoptosis."

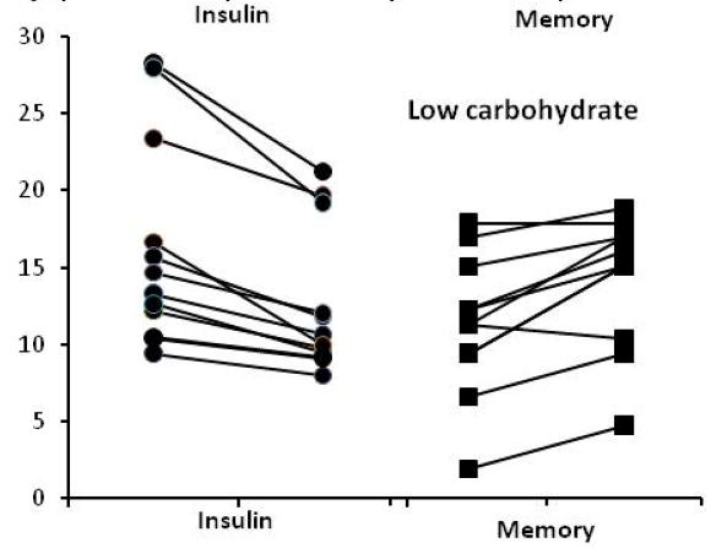
Krikorian, et al., 2010: "Dietary ketosis enhances memory in mild cognitive impairment"

Duration: 6 weeks
Population: 23 older adults with mild cognitive impairment, placed on either ketogenic or higher carbohydrate diets
Benefit: For ketogenic patients:

- Improved verbal memory performance
- Reductions in weight
- Reductions in waist circumference


Verbal Memory
Paired associate learning
18
16
14
12
10
8
6
4
2
0
Baseline
Final
High carb
Low carb


High carbohydrate
30
25
20
15
10
5
0
Insulin
Memory


Low carbohydrate
30
25
20
15
10
5
0
Insulin
Memory

Paoli, et al., 2011: "Effect of ketogenic mediterranean diet with phytoextracts and low carbohydrates/high-protein meals on weight, cardiovascular risk factors, body composition and diet compliance in Italian council employees"

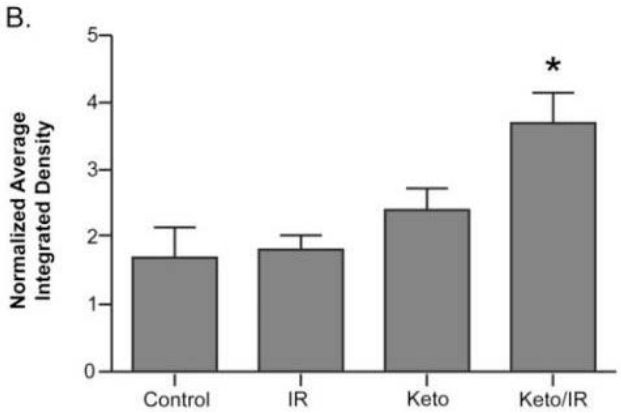
Duration: 6 weeks
Population: 106 Rome council employees with BMI 25+
Benefit:

- Significant reduction in BMI, body weight, percentage of fat mass, and waist circumference
- Reduction of total cholesterol (204 mg/dL to 181 mg/dL)
- Reduction of LDL (150 mg/dL to 136 mg/dL)
- Reduction of triglycerides (119 mg/dL to 93 mg/dL)
- Reduction of blood sugar (96 mg/dL to 91 mg/dL)
- Increase in HDL (46 mg/dL to 52 mg/dL)

Allen, et al., 2013: "Ketogenic Diets Enhance Oxidative Stress and Radio-Chemo-Therapy Responses in Lung Cancer Xenografts"

Animal Model
Population: Mice bearing NCI-H292 and A549 lung cancer xenograft
Benefit:

- Ketogenic diet plus radiation resulted in slower tumor growth in both relative to radiation alone
- Ketogenic diet alone didn't result in any inhibition of tumor growth, relative to control
- Ketogenic diet slowed tumor growth when combined with carboplatin and radiation, relative to control
- Tumors from animals given ketogenic diet plus radiation demonstrated increases in oxidative damage mediated by lipid peroxidation



KD combined with radiation increases 4HNE-modified proteins in H292 mouse lung cancer xenografts

Phelps, et al., 2013: "The ketogenic diet for type II bipolar disorder"

Duration: 2 and 3 years
Population: 2 bipolar women
Benefit:

- "Both experienced mood stabilization that exceeded that achieved with medication; experienced a significant subjective improvement that was distinctly related to ketosis; and tolerated the diet well"
- No significant adverse effects for either woman

Sumithran, et al., 2013: "Ketosis and appetite-mediating nutrients and hormones after weight loss"

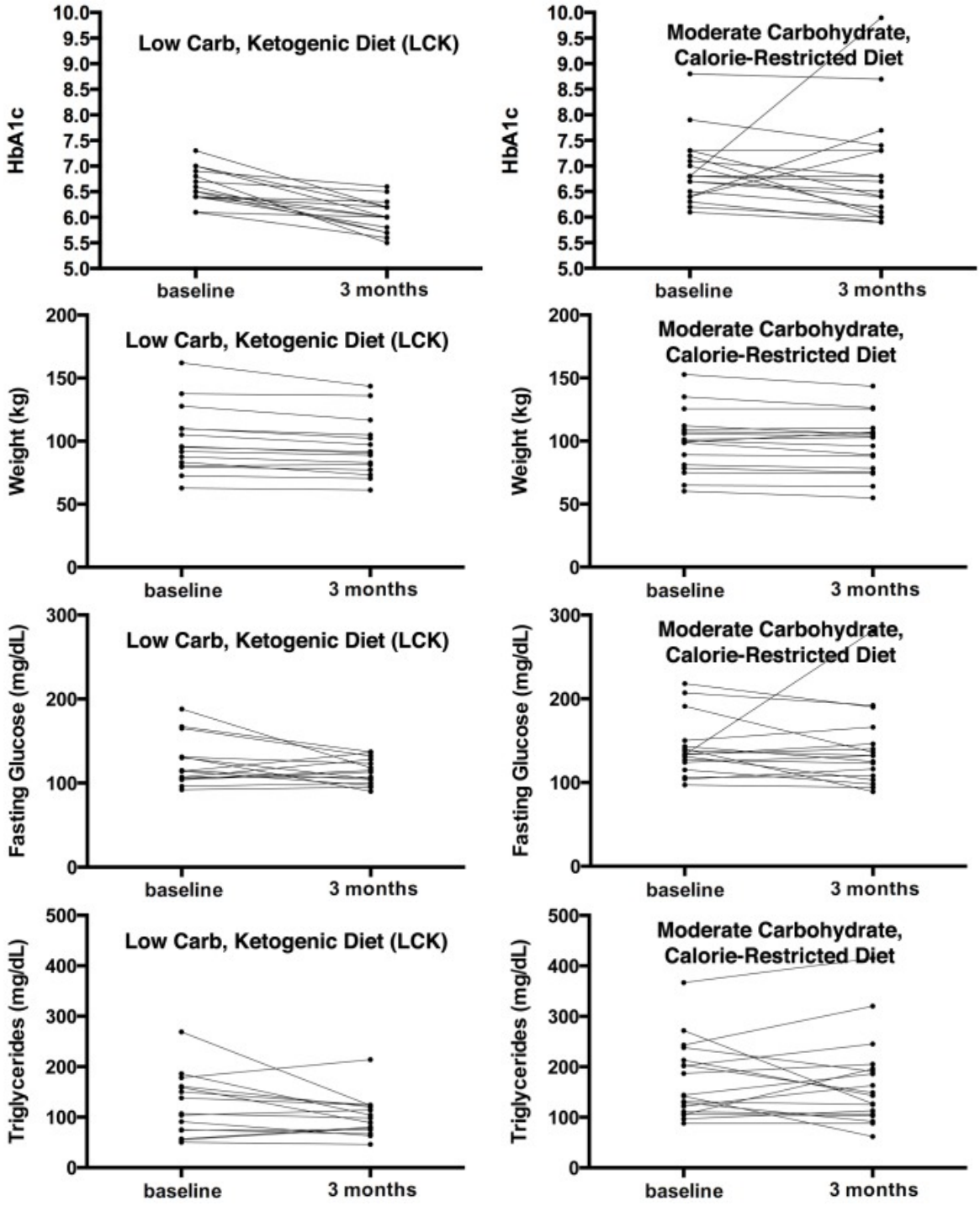
Duration: 8 weeks
Population: 39 nondiabetic, non-obese adults
Benefit:

- Lost 13% of initial weight
- Fasting β-hydroxybutyrate fell
- Suppression of weight-loss-induced increase in ghrelin
- Subjective ratings of appetite were lower by end of diet period

Saslow, et al., 2014: "A Randomized Pilot Trial of a Moderate Carbohydrate Diet Compared to a Very Low Carbohydrate Diet in Overweight or Obese Individuals with Type 2 Diabetes Mellitus or Prediabetes"

Duration: 3 months
Population: 16 patients on ketogenic diet, 18 on American Diabetes Association diet
Benefit:

- HbA1c decreased 0.6% for ketogenic dieters
- 44% of ketogenic group discontinued one or more diabetes medications
- Ketogenic group lost 5.5 kg, compared to 2.6 kg for moderate carbohydrate group



[Rhyu, et al., 2014: "The effects of ketogenic diet on oxidative stress and antioxidative capacity markers of Taekwondo athletes"]

Duration: 3 weeks
Population: 18 male taekwondo contestants age 15 - 18

Benefit:

- Ketogenic diet may increase blood antioxidative capacity and reduce oxidative stress in athletes

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No Advantage

(Click name for description of study and outcomes)

No difference in weight loss

- **Wing, et al., 1995**
- **Johnston, et al., 2006**
- **Rhyu, et al., 2014**

Studies in chronological order:

Wing, et al., 1995: "Cognitive effects of ketogenic weight-reducing diets"

Duration: 28 days
Population: 21 overweight women, randomized to either ketogenic or nonketogenic liquid diet
Effects: No difference in weight loss between ketogenic and non-ketogenic groups

Johnston, et al., 2006: "Ketogenic low-carbohydrate diets have no metabolic advantage over nonketogenic low-carbohydrate diets"

Duration: 6 weeks
Population: 20 adults assigned to either ketogenic (5% carbohydrate) or nonketogenic diet; 24-hour intakes strictly controlled
Effects: No significant difference between weight loss, fat loss, or insulin sensitivity between ketogenic and non-ketogenic groups

Rhyu, et al., 2014: "The effects of ketogenic diet on oxidative stress and antioxidative capacity markers of Taekwondo athletes"

Duration: 3 weeks
Population: 18 male taekwondo contestants age 15 – 18
Effects: No difference in weight loss, fat loss, or BMI between ketogenic and non-ketogenic diet groups

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Adverse Effects

(Click name for description of study and outcomes)

Gastrointestinal disturbances (diarrhea, vomiting, nausea, constipation, GER)

- Allan and Glasg., 1933
- Sirven, et al., 1999
- Coppola, et al., 2002
- Kang, et al., 2004
- Yancy, et al., 2004
- Kang, et al., 2005
- Groesbeck, et al., 2006
- Mosek, et al., 2009
- Nam, et al., 2011

Inflammation risk

- Johnston, et al., 2006

Thinning hair/hair loss

- Mady, et al., 2003

Kidney stones

- Kang, et al., 2004
- Groesbeck, et al., 2006
- Sampath, et al., 2007
- Suo, et al., 2013

Muscle cramps or weakness

- Yancy, et al., 2004

Hypoglycemia

- Coppola, et al., 2002

Low platelet count

- Suo, et al., 2013

Impaired concentration/cognition

- Wing, et al., 1995
- Sirven, et al., 1999

Impaired mood

- Coppola, et al., 2002
- Brinkworth, et al., 2009

Renal tubular acidosis

- Ballaban-Gil, et al., 1998

Nutrient deficiency; disordered mineral metabolism
- Hoyt and Billson, 1979 **(Thiamine)**
- Hahn, et al., 1979 **(Vitamin D and calcium)**
- Bergqvist, 2003 **(Selenium)**
- Bank, et al., 2008 **(Selenium)**
- Willmott and Bryan, 2008 **(Vitamin C/scurvy)**
- Hawkes and Levine, 2014

Poor growth in children
- Williams, et al., 2002
- Vining, et al., 2002
- Mady, et al., 2003
- Groesbeck, et al., 2006
- Bergqvist, et al., 2008
- Kim, et al., 2013

Skeletal fracture
- Groesbeck, et al., 2006

Osteopenia/osteoporosis
- Hahn, et al., 1979
- Kang, et al., 2004
- Bergqvist, et al., 2008

Increased bruising
- Berry-Kravis, et al., 2001

Sepsis, infection, bacteria overgrowth
- Coppola, et al., 2002
- Kang, et al., 2004
- Kang, et al., 2005

Pneumonia
- Kang, et al., 2004
- Kang, et al., 2005
- Nam, et al., 2011
- Suo, et al., 2013

Acute pancreatitis
- Stewart, et al., 2001
- Kang, et al., 2004
- Kang, et al., 2005

Long QT intervals

- Best, et al., 2000
- Bank, et al., 2008

Cardiomyopathy

- Best, et al., 2000
- Bergqvist, 2003
- Kang, et al., 2004
- Bank, et al., 2008
- Sirikonda, et al., 2012

Shift towards atherogenic lipid profiles (including hypercholesterolemia and hypertriglyceridemia)

- Sirven, et al., 1999
- Coppola, et al., 2002
- Kwiterovich, et al., 2003
- Kang, et al., 2004
- Yancy, et al., 2004
- Johnston, et al., 2006
- Nam, et al., 2011

Heart arrhythmia

- Johnston, et al., 2006

Myocardial infarction

- Sirven, et al., 1999

Menstrual irregularities

- Sirven, et al., 1999
- Mady, et al., 2003

Death

- Stewart, et al., 2001
- Kang, et al., 2004
- Kang, et al., 2005
- Bank, et al., 2008
- Suo, et al., 2013

Studies in chronological order:

Ellis, 1931: "Some Effects of a Ketogenic Diet"

Duration: Long enough for ketosis to be produced
Population: 20 children age 3 – 8 with various health conditions; ketogenic diet included olive oil, fried fish or sardines, "top milk," bran biscuits, one slice of white bread, butter, minced beef, cabbage, and fat ham or bacon
Adverse Effects:

- Carbohydrate intolerance/failed glucose tolerance tests after adoption of ketogenic diet

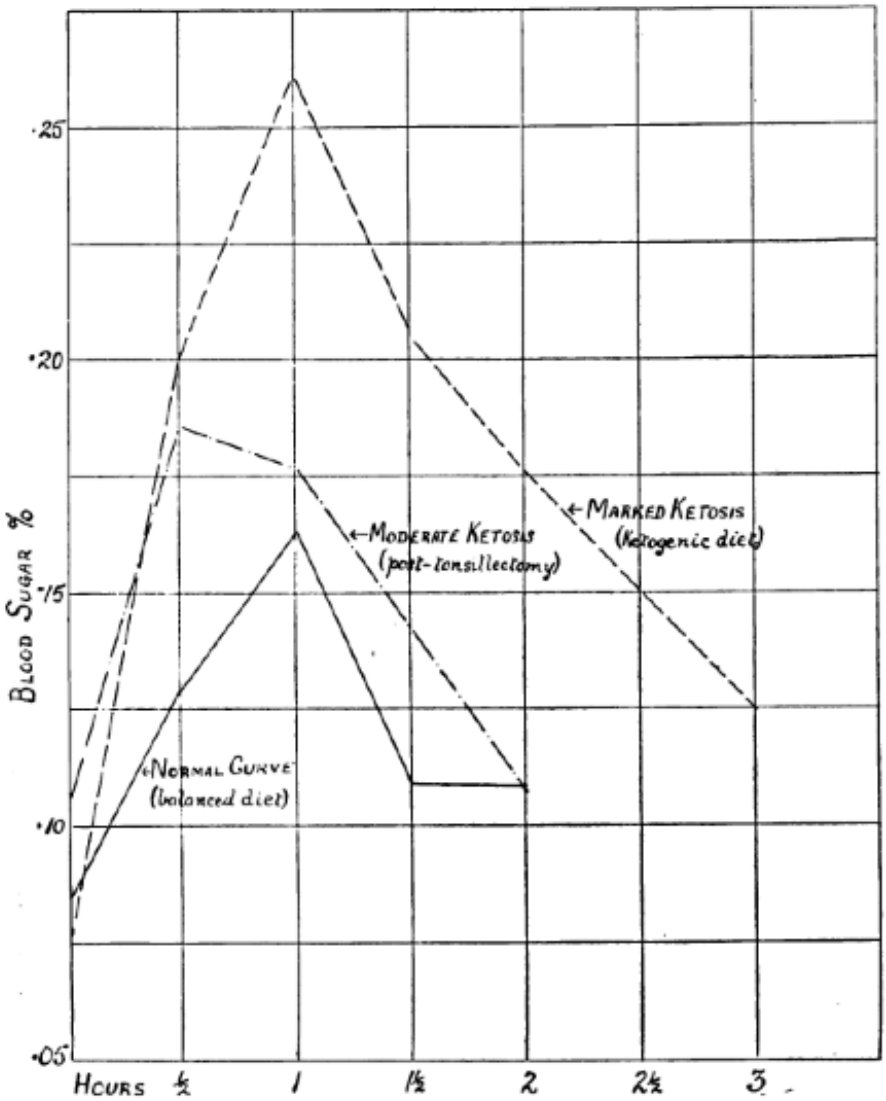


Fig. 1. Effect of ketosis on the blood sugar curve. L. R., weight 36 lb. Age 6 years. 20 grm. glucose in 50 c cm. water.

Allan and Glasg., 1933: "The ketogenic diet in epilepsy"

Population: 20 patients with idiopathic epilepsy; fed ketogenic diet of bacon, butter, cheese, cream, meat, cod liver oil, vegetables (sprouts, cabbage, tomato, cauliflower, swede, and lettuce), tea, eggs, and ½ oz of bread

Adverse Effects: Constipation, treated by weekly doses of magnesium sulphate

Hoyt and Billson, 1979: "Optic neuropathy in ketogenic diet"

Case studies:

- 2 patients eating ketogenic diet acquired symmetrical, bilateral optic neuropathy
- Lab tests suggested thiamine deficiency
- Recovery occurred after several weeks of supplementing with thiamine
- Supplementation with B vitamins advised for ketogenic dieters

Hahn, et al., 1979: "Disordered mineral metabolism produced by ketogenic diet therapy"

Duration: Keto diet for average of 2.5 years
Population: 5 children on ketogenic diet vs. 18 on anticonvulsant drugs and 15 normal controls
Adverse Effects:

- Ketogenic dieters had vitamin D deficiency osteomalacia
- Decreased serum 25-hydroxyvitamin D and calcium concentrations
- Elevated serum alkaline phosphatase and parathyroid hormone concentrations
- Decreased urinary calcium and increased urinary hydroxyproline excretion
- Decreased bone mass ("significantly greater" reduction in bone mass than the other groups)
- Improved after 5000 IU/day supplementation of vitamin D
- "These results suggest that ketogenic diet and anticonvulsant drug therapy have additive deleterious effects on bone mass"

Wing, et al., 1995: "Cognitive effects of ketogenic weight-reducing diets"

Duration: 28 days
Population: 21 overweight women, randomized to either ketogenic or nonketogenic liquid diet
Adverse Effects:

- Ketogenic group saw decreased performance on the trail making task, a neuropsychological test that requires higher order mental processing and flexibility

- Worsening in performance was observed primarily between baseline and week one of the ketogenic diet

Ballaban-Gil, et al., 1998: "Complications of the ketogenic diet"

Duration: 22 months of monitoring
Population: 52 children, ages 1.5 – 16 years; eating ketogenic diet per Johns Hopkins Hospital protocol
Adverse Effects:

- 5 children (10%) experienced serious adverse effects
- 2 children developed severe hypoproteinemia within 4 weeks of starting the diet; one of them also developed lipemia and hemolytic anemia
- 1 developed Fanconi's renal tubular acidosis within one month on the diet
- 2 children had increases in liver function tests, one during the initiation phase and one 13 months later

Case 1:

- 2.5-year-old boy
- After 21 days on keto diet, admitted to hospital with presacral and periorbital edema, along with hemolytic anemia; platelet count was above 1 million and white blood cell count was 25,700
- Treated with blood transfusions and taken off keto diet
- Within 1 week of starting high protein non-keto diet, edema and abnormal lab values returned to normal

Case 2:

- 22-month boy
- 28 days after starting keto, had lost 0.77 kg despite multiple increases in calorie intake; serum protein fell from baseline 6.3 g/dl to 4.4 g/dl
- Put on high-protein diet and weight an serum protein increased

Case 3:

- 12-year-old girl
- Approximately 3 months after being switched to traditional ketogenic diet, was hospitalized with Fanconi's renal tubular acidosis
- Supplemented with potassium and bicarbonate supplements and intravenous rehydration; improved within 1 month

Case 4:

- 6-year-old boy
- 7 months after reinitiation of ketogenic diet, developed viral gastroenteritis and admitted to hospital; low serum carnitine levels
- VPA discontinued and carnitine supplementation began; was better within 2 weeks

Sirven, et al., 1999: "The ketogenic diet for intractable epilepsy in adults: preliminary results"

Duration: 8+ months
Population: 11 adults (9 women, 2 men) ages 19 – 45 years, treated with ketogenic diet of 4:1 fat/non-fat ratio; no medication changes while on diet
Adverse Effects:

- All 11 people: gastrointestinal complaints such as constipation and bloating
- All 9 female patients: menstrual irregularities (missed or irregular cycles)
- 8 patients: reported hunger
- 2 patients: impaired concentration (7 reported improved mood and cognition)
- Unfavorable blood lipid effects: triglycerides and LDL cholesterol both increased in nearly all patients
    - Trigs rose from baseline average of 190 mg/dL to 208 mg/dL
    - Cholesterol rose from baseline average of 208 mg/dL to 291 mg/dL
    - Cholesterol/HDL ratio rose from 3.8 at baseline to 5.02 (more atherogenic)
- One patient whose seizures responded poorly ended diet after 5 months, and another 5 months after termination, had a myocardial infarction (cholesterol/HDL ratio had risen in this patient)

Supplementation: "Vitamins, phosphorus, calcium"
Food Quality: Sample daily menu provided:

- (Breakfast) 2 medium eggs, 1 sausage patty, butter, 3 tablespoons heavy whipping cream
- (Lunch) 2 hotdogs, 2 lettuce leaves, 1 thin slice tomato, 3.5 tablespoons mayonnaise
- (Dinner) 1.5 oz chicken, ½ cup green beans, 2 teaspoons butter, 4 tablespoons vegetable oil

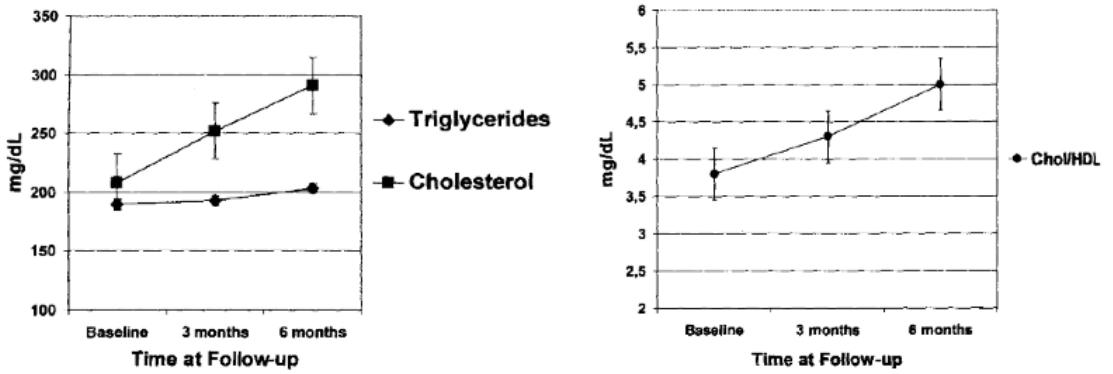


FIG. 1. The illustrated trend was seen in most patients. Serum cholesterol increased at a more rapid rate than did triglycerides. Total cholesterol/HDL ratio also increased, reflecting that serum HDL increased with serum cholesterol.

TABLE 4. *Lipid effects*

	Triglycer.			Choles.			Chol/HDL		
Patient	Baseline	3 mo	6 mo	baseline	3 mo	6 mo	baseline	3 mo	6 mo
1	262	139	417	190	293	380	3.27	4.72	6.12
2	145	172	D/C	205	262	D/C	4.36	4.22	D/C
3	542	410	300	304	320	395	8.0	7.2	7.9
4	78	54	D/C	120	187	D/C	1.9	2.67	D/C
5	41	57	68	159	206	220	2.06	2.67	4.15
6	300	320	D/C	210	235	D/C	4.37	4.4	D/C
7	138	285	270	292	369	250	5.12	7.53	6.12
8	92	100	88	167	203	246	2.31	2.36	3.11
9	130	150	149	166	200	220	2.63	3.38	3.23
10	94	144	127	267	261	324	2.84	2.83	4.5
11	262	290	D/C	207	230	D/C	5.3	5.6	D/C
Mean	190	193	203	208	252	291	3.8	4.3	5.0

Triglycer., Triglycerides; Choles., cholesterol; Triglycerides and Cholesterol units (mg/dl); Chol/HDL, Cholesterol/HDL fraction; D/C, discontinued diet.

Best, et al., 2000: "Cardiac complications in pediatric patients on the ketogenic diet"

Population: 20 patients on ketogenic diet
Adverse Effects:

- 3 patients (15%) had prolonged QT interval
- 3 patients had evidence of cardiac chamber enlargement
- 1 patient had severe dilated cardiomyopathy

Berry-Kravis, et al., 2001: "Bruising and the ketogenic diet: evidence for diet-induced changes in platelet function"

Duration: 2 months – 3 years
Population: 51 patients on ketogenic diet for epilepsy
Adverse Effects:

- 16 patients (31.4%) experienced increased bruising or other minor bleeding
- 5 patients had prolonged bleeding times
- 6 patients had diminished responsiveness to various platelet aggregating agents
- Preexisting bleeding tendencies may be amplified by ketogenic diet's effects on platelet function

Patient	Symptoms	Seizure Type	AEDs
1	Great increase in bruising when started diet, multiple large palpable bruises on exam	PM, M, GTC	PB, DPH, LTG, CLON
2	Mild increase in bruising on diet	PM, M, GTC	PB, DPH, LTG
3	Extensive multiple bruises for 2-week period only after on diet for several months	PC, GTC	
4	Dramatic increase in bruising after 1.5 months on diet, ear bleeding	PC, GTC	CBZ
5	Gradual increase in bruising since started diet, mild bruising on exam	D, AA	
6	Increased bruising since started diet, mild bruising on exams	D, M, GTC	PB, CLON
7	Increased bruising since started diet, some bruising on exams	PC, GTC, M	VPA, CBZ, TPM
8	Increased bruising from diet initiation	PC, M	VPA
9	Increased bruising from diet initiation, mild to moderate bruises on exams	PM, PC, GTC	LTG
10	Major increase in bruising while on diet, large bruises on exams	LGS	
11	Frequent nosebleeds started at about 2 months on diet, some increase in bruising	PM, GTC	CBZ
12	Increased bruising from diet initiation	M	VPA
13	Large increase in bruising and nose-bleeds from diet initiation, many large bruises on exams	PC, GTC	LTG
14	Mild consistent increase in bruises while on diet, few small bruises on exams	AA, GTC, D	
15	Two weeks with extensive bruising then resolved	PC	CBZ
16	Increased bruising on thighs while on diet, moderate size bruises on legs on exams	D, GTC	

Stewart, et al., 2001: "Acute pancreatitis causing death in a child on the ketogenic diet"

Case report:

- 9-year-old girl consuming ketogenic diet
- Presented at ER in coma with "decreased respiratory effort and shock, requiring resuscitation"
- Had cardiac arrest and died
- Postmortem examination showed hemorrhagic pancreatitis, likely caused by hypertriglyceridemia from ketogenic diet

Coppola, et al., 2002: "The ketogenic diet in children, adolescents and young adults with refractory epilepsy: an Italian multicentric experience"

Duration: 1 – 18 months
Population: 56 young patients, ages 1 – 23, with drug resistant epilepsy; placed on 4:1 ketogenic diet with calories adjusted to avoid weight loss or gain
Adverse Effects: Adverse reactions in 32 patients:

- 3 people had acute episodic diarrhea
- 10 people had severe constipation
- 9 people had drowsiness
- 6 people had episodes of vomiting
- 4 patients had recurrent abdominal pain
- 9 patients had irritability
- 2 patients had hyporexia
- 4 patients had hypoglycemia episodes
- 1 patient had severe acidosis and ketonemia
- 2 patients had oral candidosis
- 8 patients had hyperlipidemia

Williams, et al., 2002: "Growth Retardation in Children with Epilepsy on the Ketogenic Diet"

Duration: At least 6 months; retrospective chart review
Population: 21 children with intractable seizures
Adverse Effects: Decrease in weight and height percentile over the course of the study (average 1.2 years)

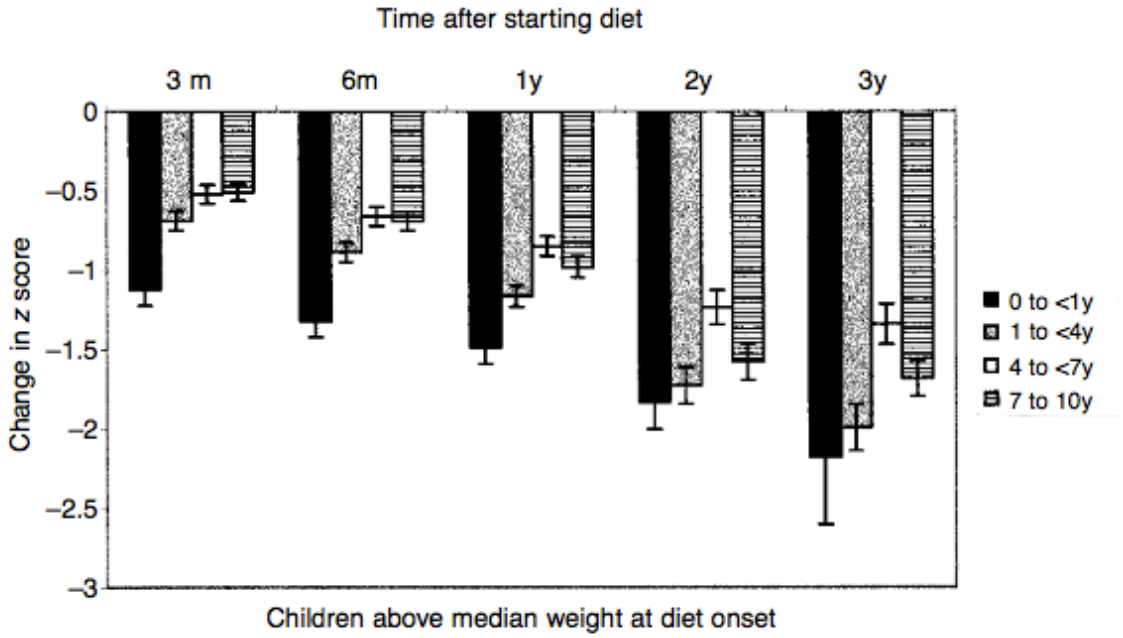
- Average weight percentile dropped from 44.3 to 39.1
- Average height percentile dropped from 47.0 to 35.4

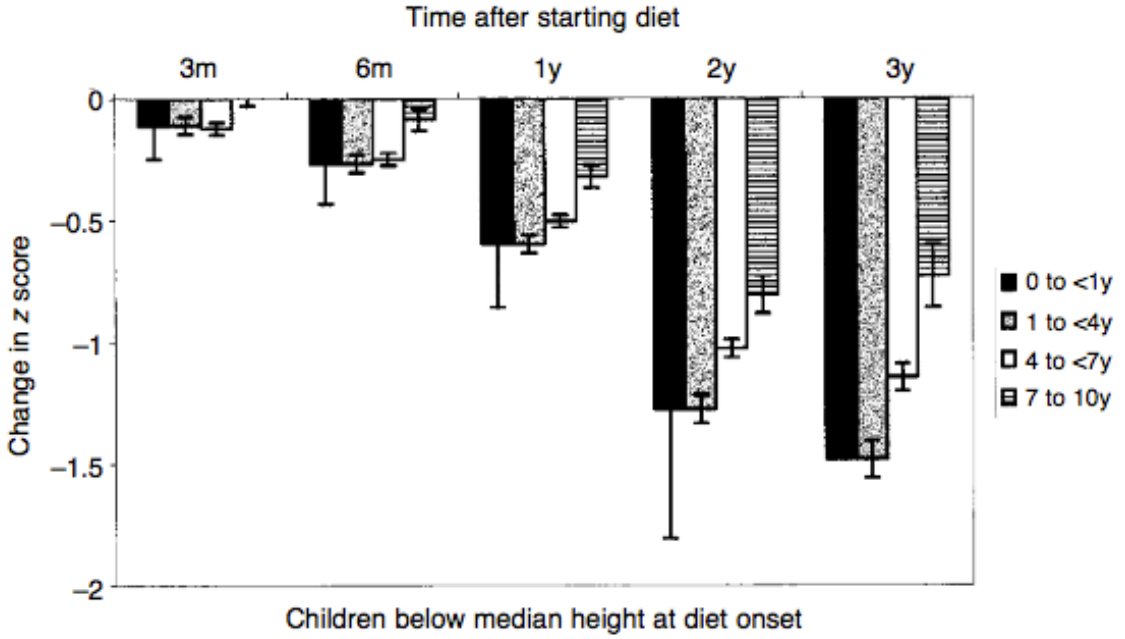
Vining, et al., 2002: "Growth of children on the ketogenic diet"

Duration: Average 308 days of follow-up
Population: 237 children (aged 2 months to 9 years 10 months) placed on ketogenic diet for intractable seizure
Adverse Effects: Poor growth among very young children; continually declining weight *z* scores among children who started diet above median weight for age

- Rapid drop in weight *z* scores in first 3 months

- After 3 months, decreased score remained constant for children who started diet below median weight for age; continued dropping for children who started above median
- Small decrease in height *z* scores in first 6 months; larger changes by 2 years

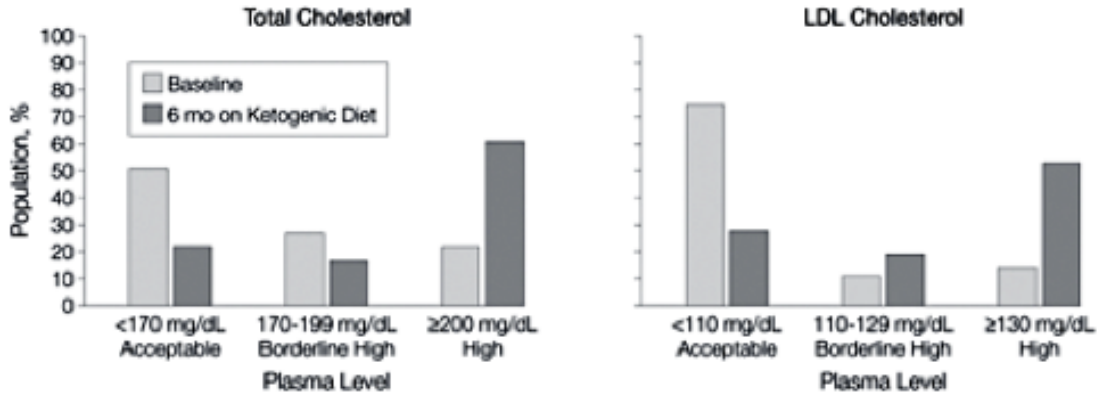


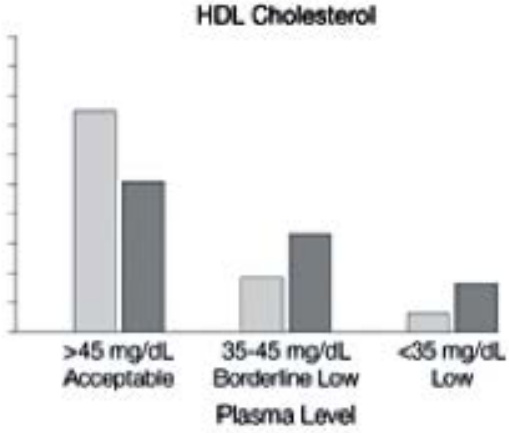


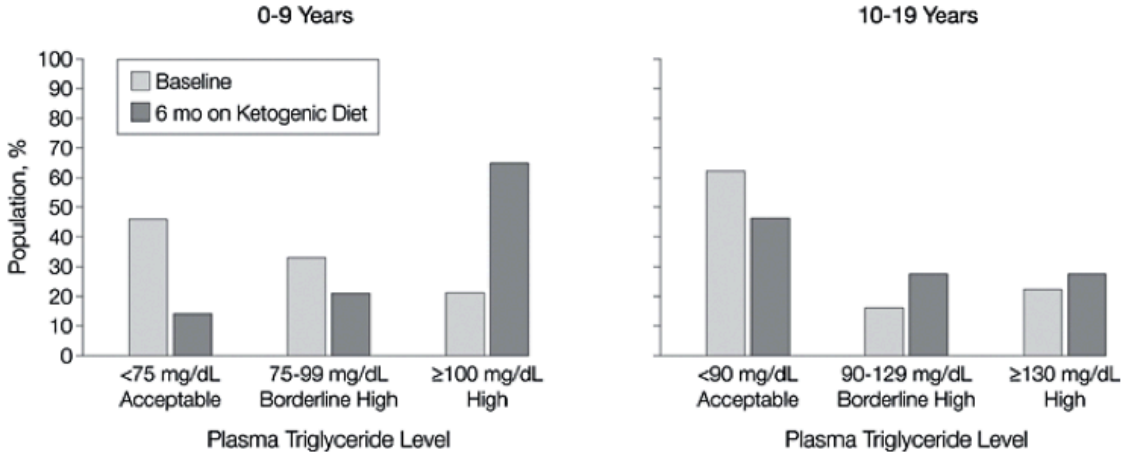
Kwiterovich, et al., 2003: "Effect of a High-Fat Ketogenic Diet on Plasma Levels of Lipids, Lipoproteins, and Apolipoproteins in Children"

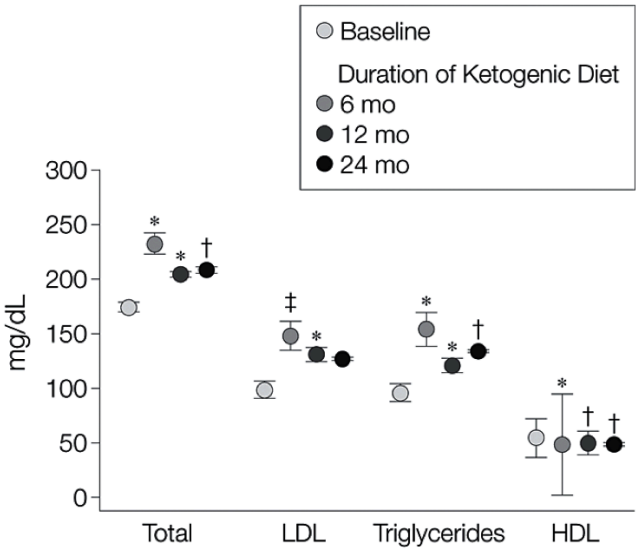
Duration: 6 months, prospective cohort study
Population: 141 children and young adults, aged 4 months – 20 years, placed on ketogenic diet for seizure control
Adverse Effects:

- After 6 months, average total cholesterol significantly increased (58 mg/dL higher than baseline)
- Average LDL significantly increased to 148 mg/dL (50 mg/dL higher than baseline); remained higher at both 12 and 24 month follow-ups
- VLDL increased (8 mg/dL) and non-HDL cholesterol increased (63 mg/dL)
- Triglycerides significantly increased (58 mg/dL higher than baseline)
- Total apoB significantly increased (49 mg/dL higher than baseline)
- Mean HDL cholesterol significantly decreased (-7 mg/dL compared to baseline); remained lower at both 12 and 24 month follow-ups
- "A high-fat ketogenic diet produced significant increases in the atherogenic apoB–containing lipoproteins and a decrease in the antiatherogenic HDL cholesterol. Further studies are necessary to determine if such a diet adversely affects endothelial vascular function and promotes inflammation and formation of atherosclerotic lesions"
- After embarking on diet, only 1 in 6 children had cholesterol or triglyceride levels in the acceptable range for their age group




HDL Cholesterol
>45 mg/dL
Acceptable
35-45 mg/dL
Borderline Low
<35 mg/dL
Low
Plasma Level


0-9 Years
10-19 Years
Baseline
6 mo on Ketogenic Diet
Population, %
100
90
80
70
60
50
40
30
20
10
0
<75 mg/dL
Acceptable
75-99 mg/dL
Borderline High
≥100 mg/dL
High
<90 mg/dL
Acceptable
90-129 mg/dL
Borderline High
≥130 mg/dL
High
Plasma Triglyceride Level
Plasma Triglyceride Level


Baseline
Duration of Ketogenic Diet
6 mo
12 mo
24 mo
mg/dL
300
250
200
150
100
50
0
Total
LDL
Triglycerides
HDL

Bergqvist, 2003: "Selenium Deficiency Associated with Cardiomyopathy: A Complication of the Ketogenic Diet"

Case Report:

- 13-year-old girl, on ketogenic diet since age 9
- Supplemented with daily multivitamin without trace elements, 250 mg phosphorus, and 500 mg of elemental calcium
- Clinic appointment revealed high cholesterol and "undetectable" whole-blood selenium
- Echocardiogram showed dilated cardiomyopathy
- Weaned off keto diet and given selenium supplementation: cardiac function normalized after 2 years

Additional Cases:

- 40 additional children had selenium levels tested
- 8 children had selenium levels below reference range

Mady, et al., 2003: "The Ketogenic Diet: Adolescents Can Do It, Too"

Duration: 6 months; average diet duration 1.2 years
Population: 45 epileptics, aged 12 – 19 years
Adverse Effects:

- 9 girls (45% of female participants) reported menstrual problems, only 4 of whom had lost weight
    - 6 experienced amenorrhea
    - 3 experienced delayed puberty
    - 1 girl experienced menorrhagia after diet discontinuation
    - 8 had menses return to normal after diet discontinuation
- 2 participants reported increased bruising or bleeding
- 2 participants reported thinning hair and/or hair loss
- 2 participants gave subjective reports of stunted growth

Yancy, et al., 2004: "A Low-Carbohydrate, Ketogenic Diet versus a Low-Fat Diet To Treat Obesity and Hyperlipidemia: A Randomized, Controlled Trial"

Duration: 24 weeks
Population: 120 overweight, hyperlipidemic adults placed on either ketogenic or low-fat, low-cholesterol diet
Adverse Effects:

- 2 people dropped out due to elevated LDL-C (rise of 184 to 283mg/dL at 3 months, and rise of 182 to 219 mg/dL at 1 month)
- 30% had elevated LDL-C of at least 10%, compared to 16% on low fat diet

- Minor adverse effects more frequent in ketogenic group (constipation, headache, halitosis, muscle cramps, diarrhea, general weakness)

	LC Diet	LF Diet	P
Constipation	68%	35%	<0.001
Headache	60%	40%	0.03
Halitosis	38%	8%	<0.001
Muscle cramps	35%	7%	<0.001
Diarrhea	23%	7%	0.02
General Weakness	25%	8%	0.01

Kang, et al., 2004: "Early- and late-onset complications of the ketogenic diet for intractable epilepsy"

Duration: At least 1 year; 6 year average
Population: 129 patients at epilepsy center (infants, children, and adolescents); ketogenic diet supplemented with multivitamins, calcium (30 mg per kg of body weight daily), vitamin D (40 IU per kg of body weight daily), L-Carnitine (66 mg per kg of body weight daily)
Short-Term Adverse Effects (before 4 weeks)

- Nausea, vomiting, diarrhea; associated with gastritis and fat intolerance (50 people)
- Various infectious diseases such as pneumonia, cystitis, and non-specific febrile illnesses (12 people)
- Lipoid pneumonia due to aspiration (3 people)
- Hypertriglyceridemia (35 people)
- Hypercholesterolemia (19 people)
- Symptomatic hypoglycemia (9 people)
- Hypoproteinemia (7 people)
- Low concentrations of high-density lipoprotein (5 people)
- Hepatitis (3 people)
- Hyperuricemia (34 people)
- Acute pancreatitis (1 person)
- Persistent metabolic acidosis (1 person)
- Repetetive hyponatremia (6 people)

Long-Term Adverse Effects (beyond 4 weeks):

- Late-onset gastrointestinal discomfort (36 people)
- Lipoid aspiration pneumonia (6 people)
- Hypertriglyceridemia (26 people)

- Hypercholesterolemia (25 people)
- Low HDL concentrations (1 person)
- Hyperuricemia (10 people)
- Symptomatic hypoglycemia (1 person)
- Hypoproteinemia (5 people)
- Hypomagnesemia (14 people)
- Hepatitis (7 people)
- Osteopenia (19 people)
- Renal stones (4 people)
- Cardiomyopathy (1 person)
- Secondary hypocarnitinemia (2 people)
- Iron-deficiency anemia (2 people)
- 1 patient discontinued diet because of persistent and uncontrollable hypertriglyceridemia of over 1,000 mg/dL; 12 patients persisteted with triglycerides over 500 mg/dL
- 22 (17%) of patients stopped diet due to serious complications
- 4 patients died (2 of sepsis, 1 of cardiomyopathy, 1 of lipoid pneumonia)

Kang, et al., 2005: "Efficacy and Safety of the Ketogenic Diet for Intractable Childhood Epilepsy: Korean Multicentric Experience"

Duration: 1 year
Population: 199 children treated for epilepsy; 87 treated with Hopkins protocol of ketogenic diet and 112 treated with revised ketogenic protocol, both at a 4:1 ratio of fat to carbohydrates/protein
Adverse Effects:

- First 12 months: 53 patients discontinued diets due to various complications or intolerance
- 9 had gastrointestinal disturbances
- 5 had serious infectious diseases
- 3 had lipoid pneumonia due to aspiration
- 1 had persistent hypomagnesemia and tetany
- 1 had persistent metabolic acidosis
- 1 had acute pancreatitis
- 1 had hypertriglyceridemia of over 1,000 mg/dL

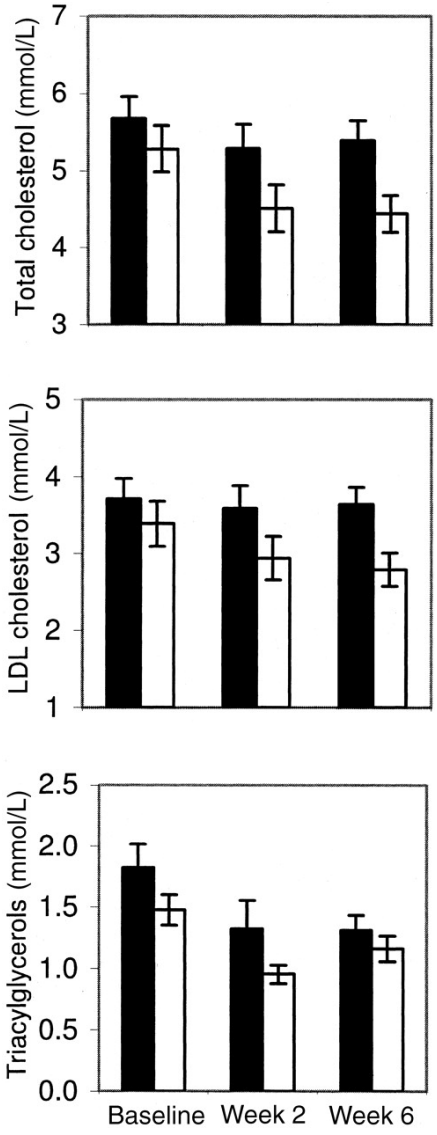
Johnston, et al., 2006: "Ketogenic low-carbohydrate diets have no metabolic advantage over nonketogenic low-carbohydrate diets"

Duration: 6 weeks

Population: 20 adults assigned to either ketogenic (5% carbohydrate) or nonketogenic diet; 24-hour intakes strictly controlled

Adverse Effects:

- Inflammatory risk (ratio of arachidonic acid to eicosapentaenoic acid in plasma phospholipids) more adversely affected by ketogenic diet than by nonketogenic diet
- HDL cholesterol fell average of 9%
- "Perceptions of vigor" lower on ketogenic diet
- One participant on ketogenic diet developed heart arrhythmias on first week of diet and dropped out
- 9% of the variation in LDL cholesterol was directly related to blood ketone concentrations, and several participants following the KLC diet had marked increases in LDL cholesterol



Groesbeck, et al., 2006: "Long-term use of the ketogenic diet in the treatment of epilepsy"

Duration: 6 – 12 years; median time on ketogenic diet 7 years 9 months
Population: 28 children and young adults (age 7 – 23 at time of chart reviews)
Adverse Effects:

- Slowed growth: 10 children at less than 10th centile for height at diet initiation; increased to 23 children after 6+ years
- 7 patients experienced kidney stones
- 6 patients experienced skeletal fracture between 6 months and 8 years (median: 1.5 years); 4 had two or more fractures at different body locations and at different times; 5 out of 6 were in the 10th centile or less for height
- 15 children experienced constipation

Sampath, et al., 2007: "Kidney stones and the ketogenic diet: Risk factors and prevention"

Duration: Retrospective cohort study of all children in clinic from 2000 through 2005; several years+ for each child
Population: 197 children
Adverse Effects:

- 13 (6.7%) of children in this study developed kidney stones after a median of 7 months
- Potassium citrate therapy preventative: 3.2% of children taking it had kidney stones versus 10% of those who did not
- *Overall:* Kidney stone prevalence ranges from 3 to 10% of ketogenic dieters, versus 1 in several thousand in general population

Table 1. Patients With Kidney Stones on the Ketogenic Diet, Started 2000-2005 (n = 13)

Patient	Age at Diet Onset, y	Ketogenic Diet Ratio	Diet Duration at Time of Stone, Months	Symptoms at Presentation*	Urine Ca/Cr at Stone	Oral Potassium Citrate Prior to Stone?	Carbonic Anhydrase Inhibitor† Use
1	1.0	3:1	1	Stone (calcium oxalate), hematuria	2.9	No	Yes
2	1.0	3:1	7	Nephrocalcinosis, hematuria	4.0	Yes	Yes
3	1.0	4:1	28	Stone fragments	1.7	Yes	Yes
4	2.5	3:1	6	Stone	0.7	No	No
5	2.5	3:1	16	Hematuria, pain	1.0	No	No
6	3.5	4:1	9	Stone, hematuria	0.3	No	No
7	4.0	3:1	4	Hematuria, pain	0.5	No	No
8	5.0	4:1	12	Stone	0.5	No	No
9	5.0	3:1	3	Stone	1.2	No	Yes
10	8.0	3:1	3	Stone (uric acid), hematuria	0.3	No	Yes
11	8.5	3:1	4	Stone fragments, hematuria	0.6	No	No
12	9.0	3:1	8	Stone (calcium carbonate)	0.4	Yes	No
13	9.0	4:1	10	Hematuria, pain	0.1	No	No

*Stone composition listed in parentheses if analyzed.
†Topiramate or zonisamide.

Willmott and Bryan, 2008: "Case report: scurvy in an epileptic child on a ketogenic diet with oral complications"

Duration: Approximately 3 years (2003 – 2006)
Population: 9-year-old girl
Adverse Effects: Scurvy

- Girl admitted to hospital with low-grade fever, persistently bleeding sockets, edema of hands and feet, petechial rash, and bruising
- Differential diagnosis included: liver disease, bleeding dyscrasia, oncological pathology, or scurvy
- Most striking finding amongst a number of investigations was a vitamin C level of 0.7 mmol/l (deficiency defined as < 11 mmol/l)
- Diagnosis of scurvy was made; 2 months after supplementing ascorbic acid, scurvy symptoms had resolved

Bank, et al., 2008: "Sudden Cardiac Death in Association With the Ketogenic Diet"

Case Study 1:

- 11-year-old boy had been on ketogenic diet (plus a multivitamin) for 3 years; seizure-free for 1 year
- Died of complications related to torsade de pointes (a dangerous tachyarrhythmia), with documented QT prolongation; had normal QT intervals before starting ketogenic diet
- Examination after death showed cardiomyopathy consistent with selenium deficiency
- Patient had no congenital heart defect
- All first-degree relatives screened and had normal EKGs/normal QT

Case Study 2:

- 7-year-old boy on ketogenic diet since age 4
- Normal electrocardiogram before diet; no personal history of cardiac problems and no family history of prolonged QTc
- Had another electrocardiogram after 3 years on ketogenic diet and showed prolonged QTc; selenium level of 0.7 mmol/L
- Was given additional selenium supplementation
- Died suddenly at home 1 month later

Conclusions: "We believe that routine electrocardiography, echocardiography, and monitoring of serum selenium are warranted before and during the ketogenic diet."

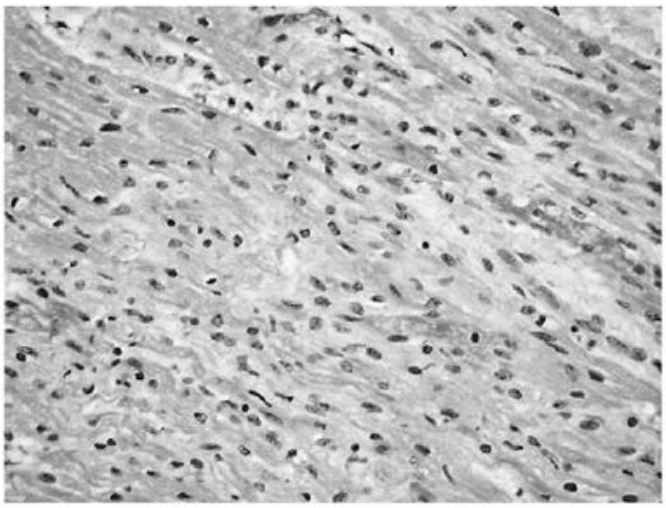


Figure 1. Case 1. Histology section showing focal necrosis of individual cardiomyocytes (myocytolysis), with a minimal lymphocytic infiltrate and some interstitial edema. Hematoxylin and eosin stain, 20×. (Other areas, not shown here, also showed signs of mild hypertrophy.)

Bergqvist, et al., 2008. "Progressive bone mineral content loss in children with intractable epilepsy treated with the ketogenic diet"

Duration: 15 months on ketogenic diet
Population: 25 children aged 1 – 14 with epilepsy (compared to cohort of 847 healthy children); eating 4:1 ketogenic diet supplemented with multivitamin (including vitamin D)
Adverse Effects:

- Suboptimal bone and growth status
- Suboptimal 25-OHD concentrations
- Declining whole-body and spine bone mineral content for both age and height
    - Whole-body and spine BMC for age declined by 0.6 *z* score per year on average
    - Whole-body BMC for height declined by 0.4 *z* score per year, and spine BMC for height declined by 0.7 *z* score per year
- On average, height and weight status declined by 0.5 *z* score per year for height and 0.2 *z* score per year for weight over 15 months
- "Bone health in children with intractable epilepsy was poor … the KD resulted in progressive loss of bone mineral content"

TABLE 2

Whole-body and spine bone mineral content (BMC) for age and height *z* scores in children with intractable epilepsy treated with the ketogenic diet for 15 mo[1]

Visit Mo	Whole-body BMC-for-age *z* score	Spine BMC-for-age *z* score	Whole-body BMC-for-height *z* score	Spine BMC-for-height *z* score
0	−1.48 ± 1.90 [23]	−0.93 ± 2.01 [19]	−1.47 ± 1.70 [23]	−0.38 ± 1.61 [19]
3	−2.10 ± 2.13 [23]	−1.49 ± 2.29 [18]	−1.69 ± 1.66 [20]	−0.25 ± 1.31 [17]
6	−2.40 ± 1.86 [15]	−1.95 ± 2.18 [15]	−1.58 ± 1.80 [12]	−0.52 ± 1.47 [11]
12	−3.08 ± 2.01 [13]	−2.31 ± 1.74 [13]	−2.27 ± 2.05 [11]	−1.39 ± 1.79 [11]
15	−2.94 ± 1.87 [13]	−2.39 ± 1.61 [12]	−2.17 ± 1.99 [11]	−1.66 ± 1.77 [10]

- ↵1 All values are $\bar{x}$ ± SD; *n* in brackets.

TABLE 4

Height, weight, and BMI *z* scores in children with intractable epilepsy treated with the ketogenic diet for 15 mo[1]

Visit mo	Height *z* score	Weight *z* score	BMI *z* score
0	−0.31 ± 1.21 [25]	−0.23 ± 1.69 [25]	−0.06 ± 1.57 [25]
3	−0.49 ± 1.19 [23]	−0.42 ± 1.61 [23]	−0.16 ± 1.53 [23]
6	−1.06 ± 1.10 [14]	−0.73 ± 1.37 [15]	0.06 ± 1.10 [14]
12	−1.37 ± 1.03 [13]	−0.99 ± 1.17 [13]	−0.16 ± 0.87 [13]
15	−1.39 ± 1.08 [13]	−1.02 ± 1.27 [13]	−0.20 ± 0.92 [13]

- ↵1 Values are $\bar{x}$ ± SD; *n* in brackets.

Mosek, et al., 2009: "Ketogenic diet treatment in adults with refractory epilepsy: A prospective pilot study"

Duration: 1 – 12 weeks follow-up; two patients completed all 12 weeks

Population: 9 adult patients enrolled (ages 18 – 45); 7 dropped out early; all placed on 90% fat ketogenic diet

Adverse Effects:

- 7 patients dropped out due to feelings of hunger, lack of efficacy, or diarrhea
- Blood lipid changes:
    - 26% rise in total cholesterol after 4 – 7 weeks and 33% rise after 11 – 12 weeks (three people)
    - LDL rose by 32% and 54% in those same time frames, with no HDL change
    - One patient's triglycerides rose to 834 mg/dL and he subsequently terminated the diet

Table 3
Lipid profile

	n	Total chol. av. ± S.D. (range) (mg/dl)	LDL av. ± S.D. (range) (mg/dl)	HDL av. ± S.D. (range) (mg/dl)	Triglycerides av. ± S.D. (range) (mg/dl)
Normal range (mg/dl)		150–200	60–160	35–70	50–175
Baseline	9	199 ± 24(172–236)	115 ± 20 (79–140)	69 ± 24 (44–120)	78 ± 36 (46–158)
4–7 weeks of KD	6	251 ± 52[a] (196–300)	152 ± 38[c] (113–167)	69 ± 22 (45–109)	218 ± 302 (78–834)
11–12 weeks of KD	3	266 ± 25[b] (238–287)	177 ± 20[d] (154–193)	70 ± 6 (62–74)	98 ± 44 (53–140)
5 weeks (av.) post-study	6	207 ± 22 (177–231)	110 ± 28 (77–161)	84 ± 23 (50–115)	67 ± 30 (33–104)

Baseline, in-study and post-study values. chol.: cholesterol; av.: average; S.D.: standard deviation; LDL: low-density lipoprotein; HDL: high-density lipoprotein; KD: ketogenic diet.

[a] $p < 0.02$ compared to baseline.
[b] $p < 0.002$ compared to baseline.
[c] $p < 0.03$ compared to baseline.
[d] $p < 0.0001$ compared to baseline.

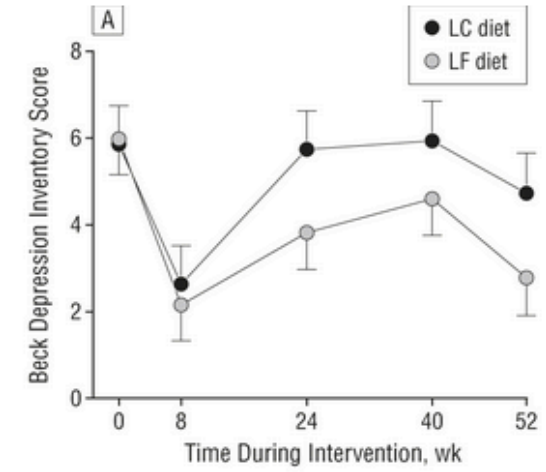
Brinkworth, et al., 2009: "Long-term Effects of a Very Low-Carbohydrate Diet and a Low-Fat Diet on Mood and Cognitive Function"

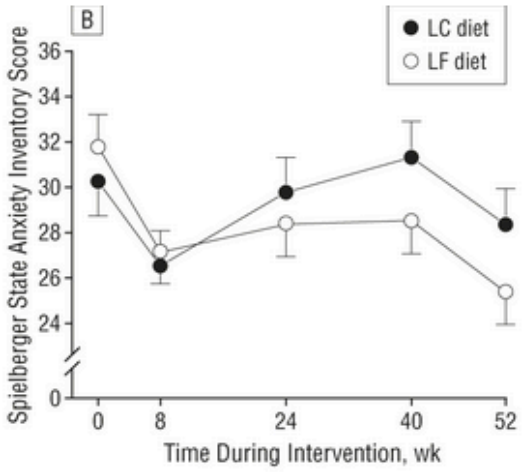
Duration: 1 year

Population: 118 adults age 24 – 64 with abdominal obesity and at least 1 additional metabolic syndrome risk factor; 57 eating ketogenic diet (4% calories from carbohydrate) and 61 eating isocaloric conventional low fat diet

Adverse Effects:

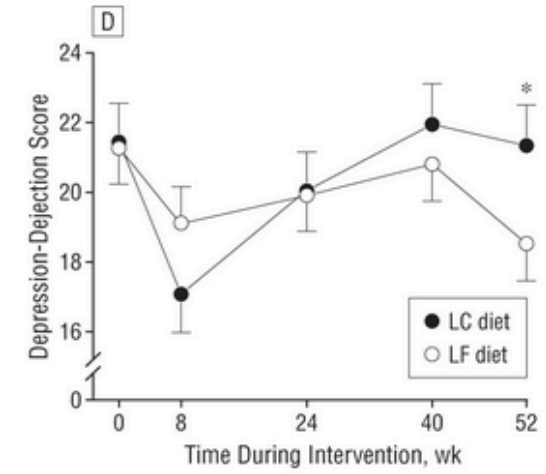
- Mood improved only initially and then rebounded towards baseline for low-carb group; sustained improvements for low-fat group
- "This outcome suggests that some aspects of the LC diet may have had detrimental effects on mood that, over the term of 1 year, negated any positive effects of weight loss"

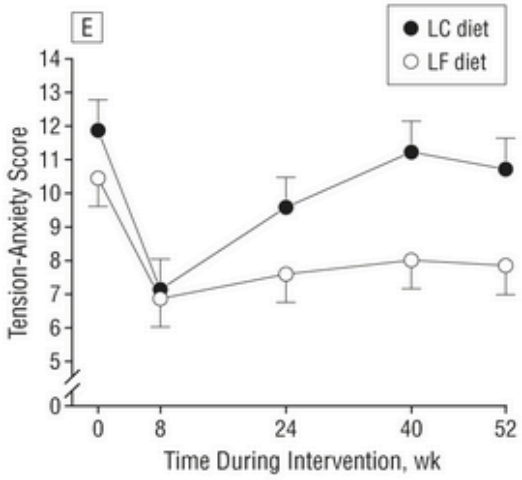


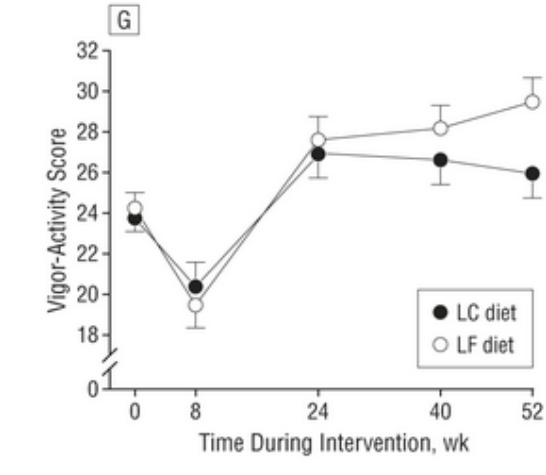


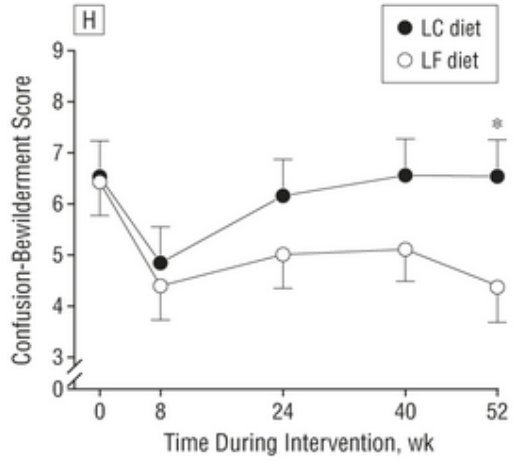
LC group	55	49	45	36	32
LF group	51	47	39	36	33

	55	49	45	36	32
	51	47	39	36	33



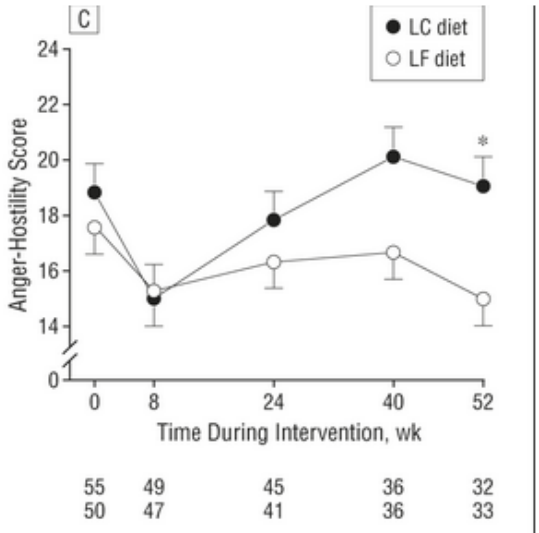


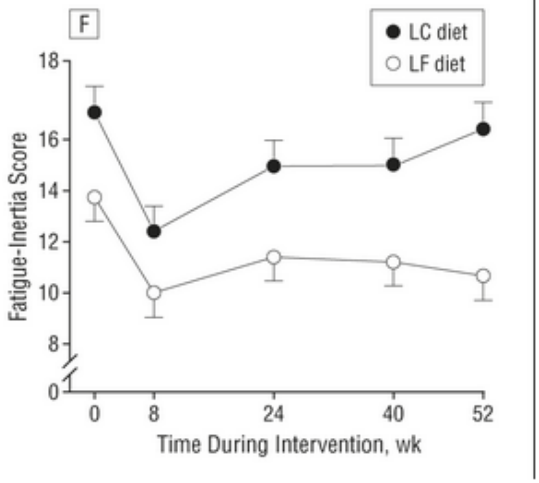




LC group	55	49	45	36	32
LF group	51	47	41	36	33

	55	49	45	36	32
	51	47	41	36	33


C
LC diet
LF diet
Anger-Hostility Score
24
22
20
18
16
14
0
*
0
8
24
40
52
Time During Intervention, wk
55 49 45 36 32
50 47 41 36 33


F
LC diet
LF diet
Fatigue-Inertia Score
18
16
14
12
10
8
0
0
8
24
40
52
Time During Intervention, wk

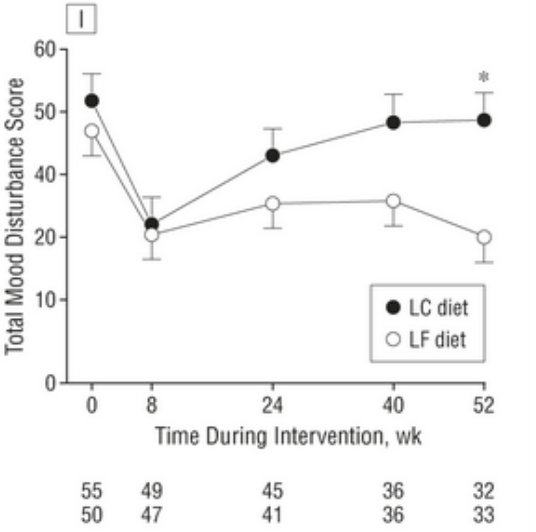

I
Total Mood Disturbance Score
60
50
40
30
20
10
0
*
LC diet
LF diet
0
8
24
40
52
Time During Intervention, wk
55 49 45 36 32
50 47 41 36 33

Table. Mixed-Effects Model of the Effects of an Energy-Restricted, Low-Carbohydrate, High-Fat (LC) Diet and a High-Carbohydrate, Low-Fat (LF) Diet Over 12 Months on Working Memory (Digit Span Backward) and Inspection Time

	Estimated Marginal Mean (SE)[a]		
	Week 0	Week 8	Week 52
Working memory			
LC diet	4.2 (0.3)	4.9 (0.3)[b]	4.8 (0.3)[b]
LF diet	3.9 (0.2)	4.7 (0.2)[b]	4.8 (0.3)[b]
Inspection time, ms			
LC diet	63.3 (2.5)	59.1 (2.5)[b]	63.1 (2.6)
LF diet	66.7 (2.3)	56.6 (2.3)[b]	63.5 (2.5)

[a] Participant numbers were as follows: 55 in the LC group and 51 in the LF group during week 0; 49 in the LC group and 47 in the LF group during week 8; and 32 in the LC group and 32 in the LF group during week 52. For working memory and inspection time, higher and lower numbers, respectively, indicate better performance for each task.

[b] $P=.01$ for time, significantly different compared with week 0.

Nam, et al., 2011: "The role of ketogenic diet in the treatment of refractory status epilepticus"

Duration: 1+ month
Population: 5 people (4 children, 1 adult) with refractory status epilepticus, placed on 4:1 ketogenic diet
Adverse Effects:

- All patients suspected to have GER
- 1 patient diagnosed with esophagitis
- 4 out of 5 patients had constipation
- 1 patient had hypertriglyceridemia
- 1 patient had aspiration pneumonia

Table 2. Results of ketogenic diet

Case	50% reduction of Sz (day)	Sz reduction on 1 mo (%)	F/U[a] (mo)	KD[b] (mo)	Seizure outcome[c]	Functional status at last follow-up	Adverse effect of KD
1	3	75	16	16	Nondisabling partial seizures, 0–5/day	Spontaneous eye open but unable to obey, bedridden	Hypertriglyceridemia, constipation, GER
2	19	100	14	1	Nondisabling partial seizures, 0–3/month	Mild mental retardation, normal daily living	Aspiration pneumonia, constipation
3	14	75	8	8	Sz-free for 1 month	Mild mental retardation, walk alone	Constipation, severe GER
4	8	90	7	5	Sz-free for 4 months	Mental retardation walk alone	Constipation
5	7	100	6	1	Sz-free for 3 months	Normal daily living	None

Sz, seizure; mo, month; F/U, follow-up; KD, ketogenic diet; GER, gastroesophageal reflux.
[a]Duration from starting KD to last follow-up.
[b]Duration of KD.
[c]Seizure outcome at last follow-up.

Sirikonda, et al., 2012: "Ketogenic Diet: Rapid Onset of Selenium Deficiency-Induced Cardiac Decompensation"

Case Report:

- 5-year-old boy on ketogenic diet for intractable seizures
- 2.5 months on ketogenic diet
- Normal selenium levels before starting diet
- Developed cardiomyopathy and ventricular tachycardia
- Rapid improvement after selenium supplementation and cessation of ketogenic diet

Kim, et al., 2013: "Catch-up growth after long-term implementation and weaning from ketogenic diet in pediatric epileptic patients"

Duration: 2 years on ketogenic diet, 1 year off of it; retrospective chart review
Population: 40 children (20 male and 20 female)
Adverse Effects:

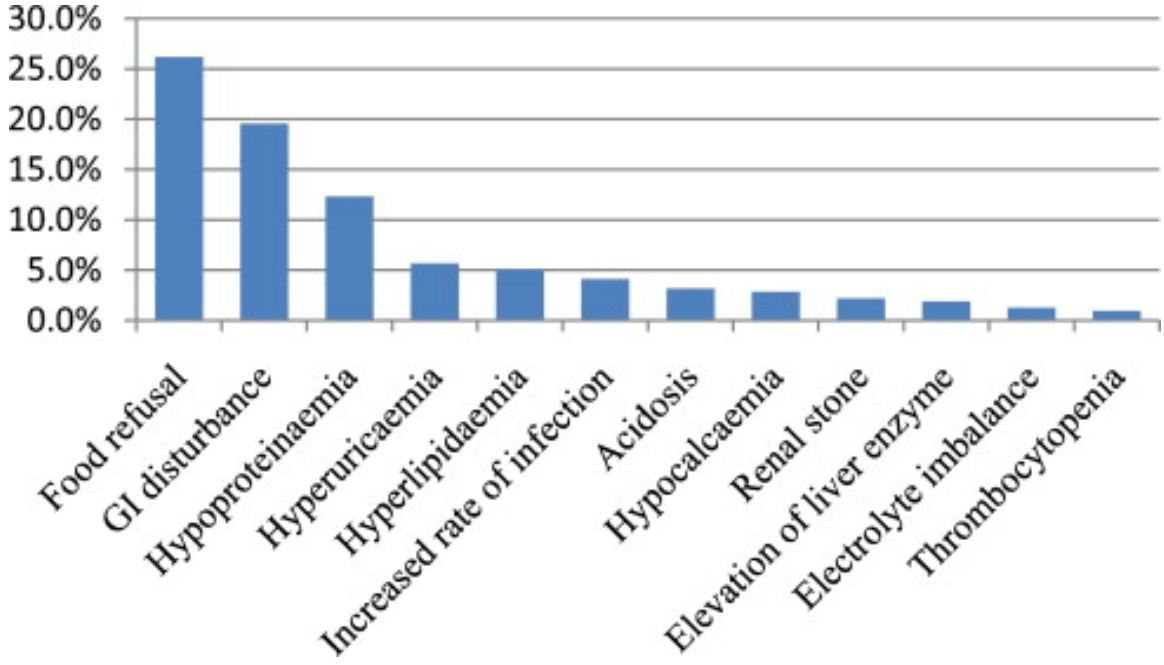
- Significant reduction in both height and weight gain after 2 years on ketogenic diet
- After discontinuing diet, significant "catch-up growth" in height and weight occurred by 1 year

	Paried difference of baseline to 2 years after KD		**Paried difference of baseline to 1 year off KD**	
	Mean ± SD	p value	Mean ± SD	p value
Height (n=40)	-1.13 ± 1.46	0.000*	-0.13 ± 1.43	0.569
Weight (n=40)	-0.56 ± 1.14	0.004*	-0.37 ± 1.20	0.060
BMI (n=32)	0.43 ± 1.48	0.111	-0.21 ± 0.93	0.21

Suo, et al., 2013: "Efficacy and safety of the ketogenic diet in Chinese children"

Duration: 3, 6, and 12-month follow-ups after starting diet
Population: 317 children eating 4:1 ketogenic diet, per Johns Hopkins Hospital protocol
Adverse Effects:

- 39 experienced hypoproteinaemia; all but one in children under 5 years old
- 7 children had renal stones
- 3 children had thrombocytopenia (low platelet count)
- 10 deaths at follow-up; 7 from children still on keto diet:
    - 2 died of pneumonia
    - 2 died from epilepsy
    - 1 fell from height
    - 2 not disclosed



Hawkes and Levine, 2014: "Ketotic Hypercalcemia: A Case Series and Description of a Novel Entity"

Duration: 6 – 12 months on ketogenic diet
Population: 3 cases: 5.5-year-old boy; 2.5-year-old boy; 4.6-year-old boy
Adverse Effects: Elevated serum calcium despite normal dietary intake of calcium and vitamin D

Mechanisms of Action Explaining Adverse Effects

(Click name for description of study and outcomes)

Sex hormones

- Rhodes, et al., 2005
- Mavropoulos, et al., 2005

Bone health and growth

- Bergqvist, et al., 2008

Inflammation/immune system

- Kim, et al., 2012 (MS)
- Husain, et al., 2013 (Cancer)
- Garbow, et al., 2011 (NAFLD)
- Fraser, et al., 2000 (RA)
- Fraser, et al., 2000 B (RA)

ApoE4

- Tikkanen, et al., 1990
- Lopez-Miranda, et al., 1994
- Bergeron and Havel, 1996
- Kobayashi, et al., 2001
- Moreno, et al., 2004
- Henderson, et al., 2009

Gut microbiome

- David, et al., 2014

Platelet function

- Berry-Kravis, et al., 2001

Studies in chronological order:

Tikkanen, et al., 1990: "Apolipoprotein E4 homozygosity predisposes to serum cholesterol elevation during high fat diet"

> **Findings:** 110 adults (ages 30 to 50); when eating low-fat diet, greater reductions in plasma cholesterol in those homozygous for the ApoE4 compared to subjects with other genotypes; ApoE4 carriers responded to the switchback diet by greater increases in plasma cholesterol (1.52 mmol/l) than others (0.92 mmol/l, p = 0.0141)
> **Mechanism:** The effect of ApoE4 genotype on plasma cholesterol is modulated by dietary fat and cholesterol intake; ApoE4 experiences greater

intestinal cholesterol absorption efficiency and more rapid hepatic clearance of dietary fat

Table 4. Changes in Total Plasma Cholesterol and Low Density Lipoprotein Cholesterol during Dietary Study

Changes	Plasma lipid	E4/E4 (n=8)	E4/E3, E3/E3, or E3/E2 (n=102)	*P*
Decrease during intervention	Cholesterol	−1.84	−1.13	0.0097
	LDL chol	−1.51	−0.91	0.0164
Increase during switchback	Cholesterol	1.52	0.92	0.0141
	LDL chol	1.17	0.68	0.0221

The values are given in mmol/l.
LDL, low density lipoprotein.

Lopez-Miranda, et al., 1994: "Effect of apolipoprotein E phenotype on diet-induced lowering of plasma low density lipoprotein cholesterol"

Findings: 133 people fed low fat or higher fat diet; ApoE4 carriers saw significantly greater LDL reduction than non-carriers after low-fat diet
Mechanism: The differential removal of triglyceride-rich particles by the liver, and additional mechanisms involving plasma compartment or extrahepatic tissues to modulate dietary response and ApoE4

TABLE 4. Plasma total cholesterol and triglycerides on each diet phase (mean ± SD)

Group	Number	High Fat	Low Fat	Change	% Change[a]
Total cholesterol (mg/dl)					
All males[b]	86	222 ± 41	191 ± 42	−31 ± 23*	−14
E3/4	10	234 ± 39	191 ± 33	−43 ± 32*	−17
		(236)	(198)	(−38)	(−16)
E3/3	60	222 ± 43	193 ± 44	−29 ± 22*	−13
		(222)	(193)	(−29)	(−13)
E2/3	13	212 ± 38	182 ± 45	−30 ± 23*	−14
		(209)	(182)	(−27)	(−13)
All females[c]	47	250 ± 39	232 ± 43	−18 ± 24*	−7
E3/4	7	262 ± 34	246 ± 39	−16 ± 16**	−6
		(273)	(253)	(−20)	(−7)
E3/3	34	249 ± 41	230 ± 46	−19 ± 26*	−8
		(244)	(227)	(−17)	(−7)
E2/3	4	233 ± 17	223 ± 27	−10 ± 17	−4
		(217)	(204)	(−13)	(−6)
Triglycerides (mg/dl)					
All males	86	124 ± 62	126 ± 42	2 ± 48	2
E3/4	10	126 ± 56	137 ± 70	11 ± 69	9
E3/3	60	127 ± 68	127 ± 55	0	0
E2/3	13	111 ± 35	118 ± 39	7 ± 21	6
All females	47	143 ± 79	148 ± 69	5 ± 57	3
E3/4	7	119 ± 34	153 ± 52	34 ± 34**	29
E3/3	34	150 ± 84	144 ± 70	−6 ± 61	−4
E2/3	4	164 ± 95	201 ± 61	37 ± 54	23

Numbers in parentheses represent adjusted values after correcting for study site, age, and BMI (see text for details).
[a]Percent change was calculated as: [High Fat] − [Low Fat]/[High Fat] × 100.
[b]Values for apoE4/4 (1), apoE2/2 (1), and apoE2/4 (1) subjects are not shown.
[c]Values for apoE4/4 (1) and apoE2/4 (1) subjects are not shown.
*$P < 0.005$; **$P < 0.05$, comparison between diet phases, paired t-test.

Bergeron and Havel, 1996: "Prolonged postprandial responses of lipids and apolipoproteins in triglyceride-rich lipoproteins of individuals expressing an apolipoprotein epsilon 4 allele"

Findings: 16 normolipidemic young men saw different postprandial responses to high-fat diet

Mechanism: "These observations suggest that clearance of intestinal and hepatogenous TRL remnants is impaired in young men with an apo E4/3 phenotype. … We speculate that the apo E on chylomicron remnants of persons with an apo E4/3phenotype may be less accessible to hepatic lipoprotein receptors than apo E from persons with an apoE3/3 phenotype. The same may apply to VLDL remnants which also appear to accumulate in persons with an apo E4/3 phenotype"

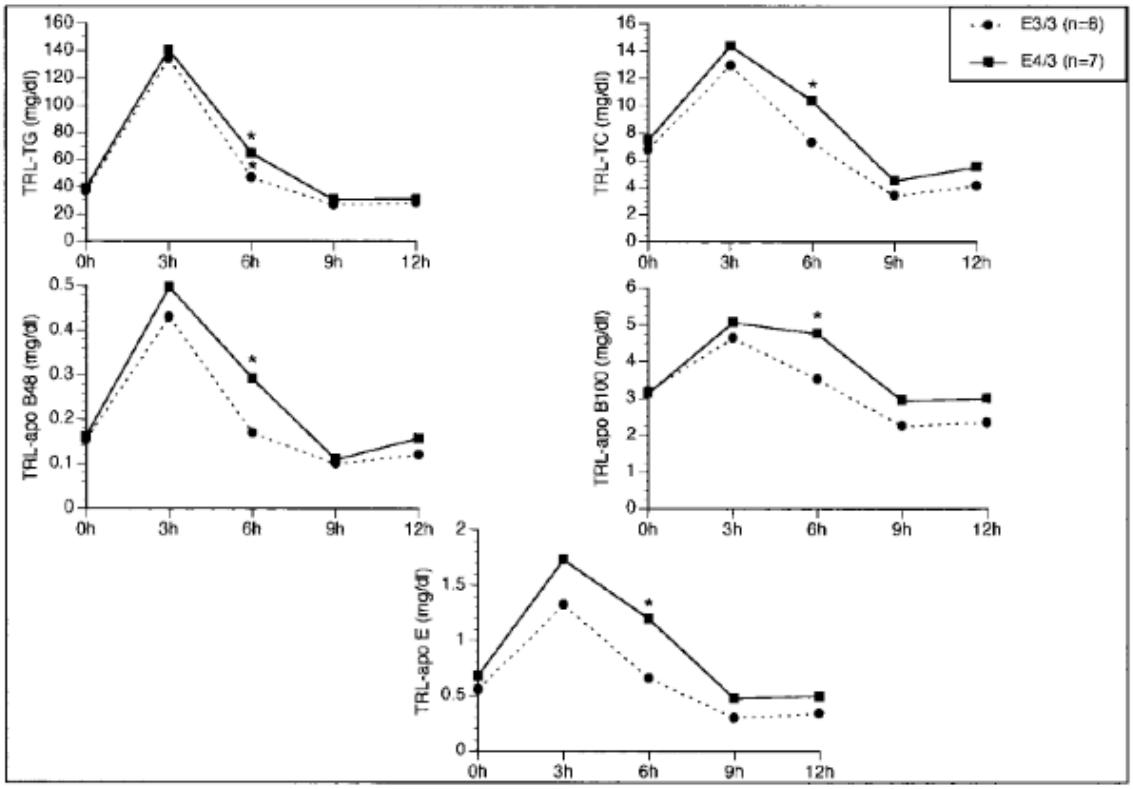


Figure 1. Mean postprandial changes in TRL triglycerides (*TG*), apo B48, cholesterol (*TC*), apo B100, and apo E in individuals with apo E3/3 and apo E4/3 phenotypes fed a PUFA-rich diet and challenge meal (day 15). All components of TRL at 3 h were significantly higher than 0 h values ($P < 0.01$). * Significantly different from 0 h values by the Wilcoxon matched pairs test ($P < 0.05$).

Fraser, et al., 2000: "Reduction in serum leptin and IGF-1 but preserved T-lymphocyte numbers and activation after a ketogenic diet in rheumatoid arthritis patients"

Findings: 13 RA patients, 7-day ketogenic diet; no significant changes in any of the clinical or laboratory measures of disease activity, or in early T-lymphocyte activation and the absolute numbers of CD4+ and CD8+ cells
Mechanism: "In RA patients several of the metabolic and hormonal responses to a ketogenic diet, such as a fall in serum IGF-1 and leptin, resemble those which occur in response to acute starvation. However, the

clinical and immunological changes which occur in response to acute starvation do not take place with a ketogenic diet and thus may be dependent upon energy and/or protein restriction."

Fraser, et al., 2000 B: "Serum levels of interleukin-6 and dehydroepiandrosterone sulphate in response to either fasting or a ketogenic diet in rheumatoid arthritis patients"

Findings: 23 RA patients, 7-day ketogenic diet versus 7-day fast: Fasting, but not the ketogenic diet, decreased serum IL-6 concentrations by 37% ($p < 0.03$) and improved disease activity at day 7. Both fasting and the ketogenic diet increased serum DHEAS levels by 34% as compared with baseline (both $p < 0.006$)
Mechanism: The fasting-induced fall in serum IL-6 may underlie the fall in CRP and ESR observed in RA patients in response to a 7-day fast.

Kobayashi, et al., 2001: "Effect of apolipoprotein E3/4 phenotype on postprandial triglycerides and retinyl palmitate metabolism in plasma from hyperlipidemic subjects in Japan"

Findings: 62 Japanese adults saw significantly higher postprandial triglycerides and retinyl palmitate in response to fatty meal among ApoE4 carriers versus non-carriers
Mechanism: "These results indicate that in Japanese population especially for men apo E phenotype E3/4 is associated with an impaired postprandial TG-rich lipoprotein metabolism relative to apo E3/3 phenotype when matched for intra-abdominal visceral fat accumulation, which has a substantial effect on the metabolism of plasma TG-rich lipoproteins."

Berry-Kravis, et al., 2001: "Bruising and the ketogenic diet: evidence for diet-induced changes in platelet function"

Findings: 51 patients on ketogenic diet for up to 3 years; experienced easy bruising and bleeding
Mechanism: "ketogenic diet-related bleeding tendency occurs in about one third of patients owing to preexisting factors defining susceptibility in combination with diet-induced depression of platelet responsiveness, possibly related to changes in platelet membrane lipid composition and/or concentration and resultant effects on function of membrane-embedded proteins"

Moreno, et al., 2004: "The Effect of Dietary Fat on LDL Size Is Influenced by Apolipoprotein E Genotype in Healthy Subjects"

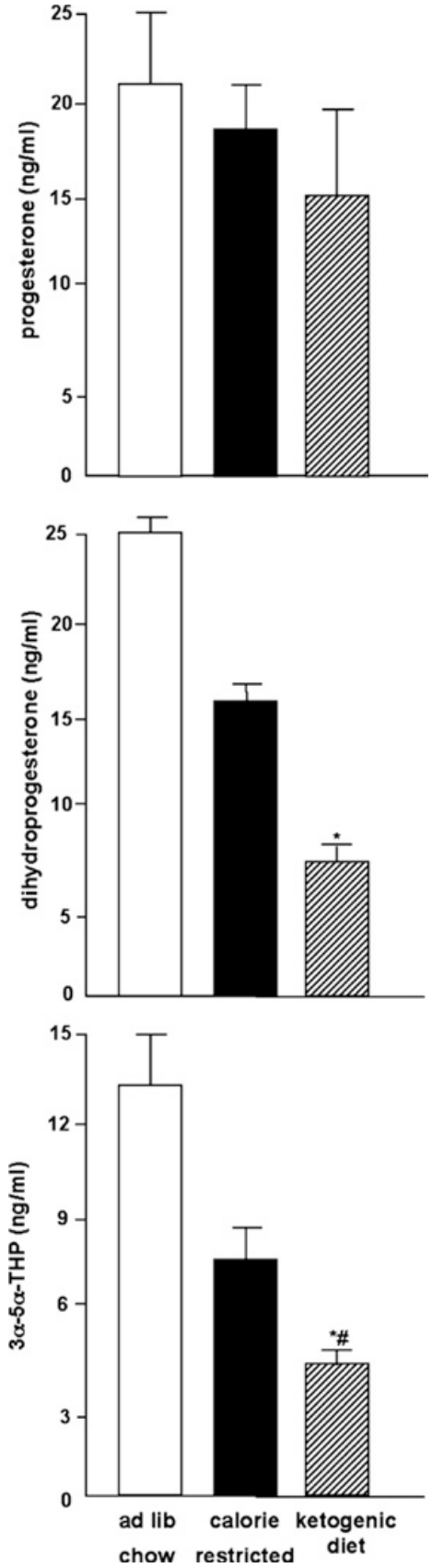
Findings: In ApoE4/3 carriers, increase in saturated fat = decreased LDL particle size and increased ApoB; for non-E4 carriers, increased saturated fat did the opposite
Mechanism: "Our results showed that replacement of a CHO diet by a MUFA diet increased the LDL-size in apoE 3/3 young healthy subjects, whereas it decreased LDL-size in apoE 4/3 subjects"

Rhodes, et al., 2005: "Ketogenic diet decreases circulating concentrations of neuroactive steroids of female rats"

Findings: Rats; 6-week ketogenic diet after weaning, compared to low-calorie diet and ad libitum:

- Decreases pregnane (progesterone, dihydroprogesterone, 3alpha,5alpha-THP) and androstane (testosterone, dihydrotestosterone, 3alpha-androstanediol)

- Pregnane and androstane, neuroactive hormones, believed to underlie antiseizure effects of ketogenic diet


progesterone (ng/ml)
25
20
15
10
5
0
dihydroprogesterone (ng/ml)
25
20
15
10
5
0
*
3α-5α-THP (ng/ml)
15
12
9
6
3
0
*#
ad lib chow
calorie restricted
ketogenic diet

Mavropoulos, et al., 2005: "The effects of a low-carbohydrate, ketogenic diet on polycystic ovary syndrome: A pilot study"

> **Findings:** Reduced free testosterone, and LH/FSH ratio in 5 women, age 18-45, ketogenic diet for 24 weeks (<20g carbohydrates, Atkins intro)
> **Mechanism:** Authors speculate mechanism is insulin

Henderson, et al., 2009: "Study of the ketogenic agent AC-I202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial"

> **Findings**: ApoE4 carriers experience less (or no) benefit from high levels of ketosis (in this study, induced by oral ketogenic compound, AC-1202) compared to non-ApoE4 carriers
> **Mechanism:** "We can only speculate on the mechanisms underlying the genotype-specific effects seen in this study, but there are reasons to suggest such an effect is not spurious. … One hypothesis is that there may be lower mitochondrial enzyme function in E4(+) versus E4(-) as noted in AD brain tissue samples. Reduced mitochondrial function may inhibit the ability of E4(+) participants to utilize ketone bodies and this may explain the apparent unresponsive-ness to AC-1202 reported here."
>
> "An alternative explanation may be a differential insulin sensitivity of AD subjects based on APOE genotype. Ketone bodies are transported into the brain by monocarboxylate transporters. Levels of monocarboxylate transporters in the microvasculature are known to be low in adult mammals, yet elevated in diabetes and in other conditions where insulin resistance occurs. The milder insulin resistance in E4(-) AD subjects may allow them to more efficiently import ketone bodies into the brain and hence respond to AC-1202."

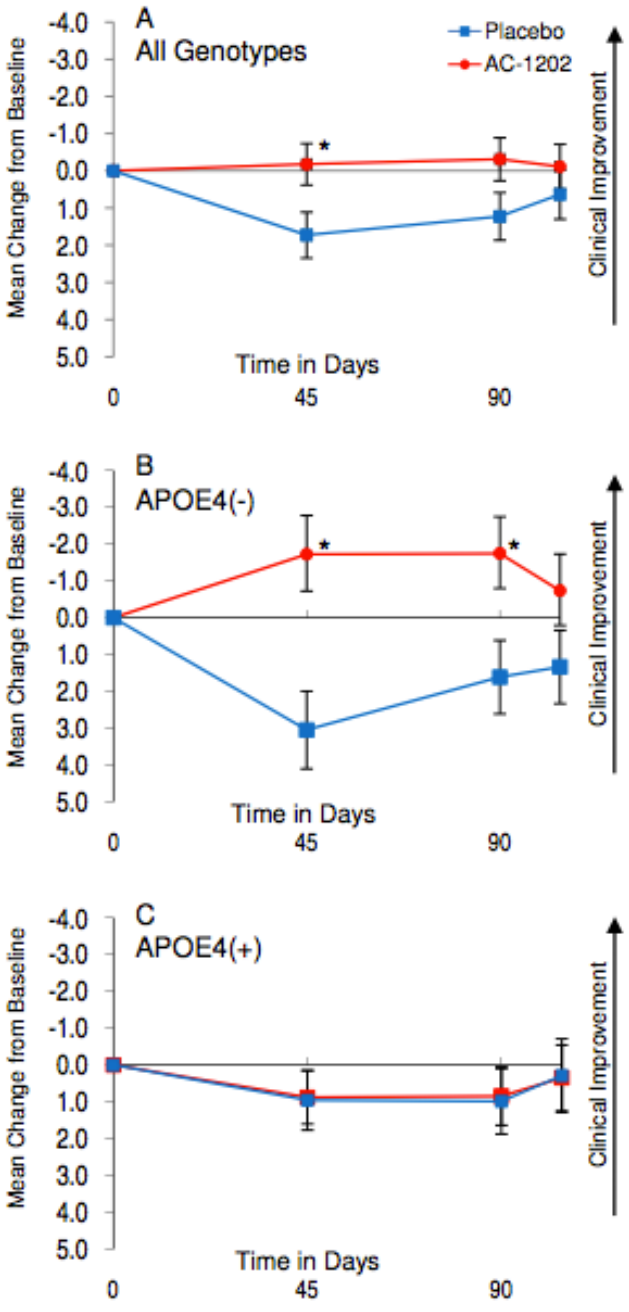

A
All Genotypes
Placebo
AC-1202
Mean Change from Baseline
-4.0
-3.0
-2.0
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
*
Clinical Improvement
Time in Days
0
45
90
B
APOE4(-)
Mean Change from Baseline
*
*
Clinical Improvement
Time in Days
0
45
90
C
APOE4(+)
Mean Change from Baseline
Clinical Improvement
Time in Days
0
45
90

Figure 2
Mean change in ADAS-Cog scores from Baseline in the ITT population w/LOCF and stratified by APOE4 carriage status. Y axis is change from Baseline. X axis is time in days. Red circles and lines represent subjects taking AC-1202. Blue squares and lines represent subjects taking Placebo. Error bars represent standard error of the mean. Asterisks (*) indicate a significant (p-value < 0.05) difference in mean change from Baseline between AC-1202 and Placebo. **A)** Intention to treat subjects (N = 77AC, N = 63PL) administered AC-1202 demonstrate a significant difference from Placebo at Day 45. **B)** Genotyped subjects lacking the APOE4 allele (APOE4(-)) (N = 29AC, N = 26PL) and administered AC-1202 demonstrate a significant difference from Placebo at Days 45 and 90. **C)** Genotyped subjects carrying the APOE4 allele (APOE4(+)) (N = 38AC, N = 31PL) do not differ from Placebo at any time point. For confidence intervals and p-values see Table 5.

Bergqvist, et al., 2008. "Progressive bone mineral content loss in children with intractable epilepsy treated with the ketogenic diet"

Duration: 15 months on ketogenic diet
Population: 25 children aged 1 – 14 with epilepsy (compared to cohort of 847 healthy children); eating 4:1 ketogenic diet supplemented with multivitamin (including vitamin D)
Mechanism:

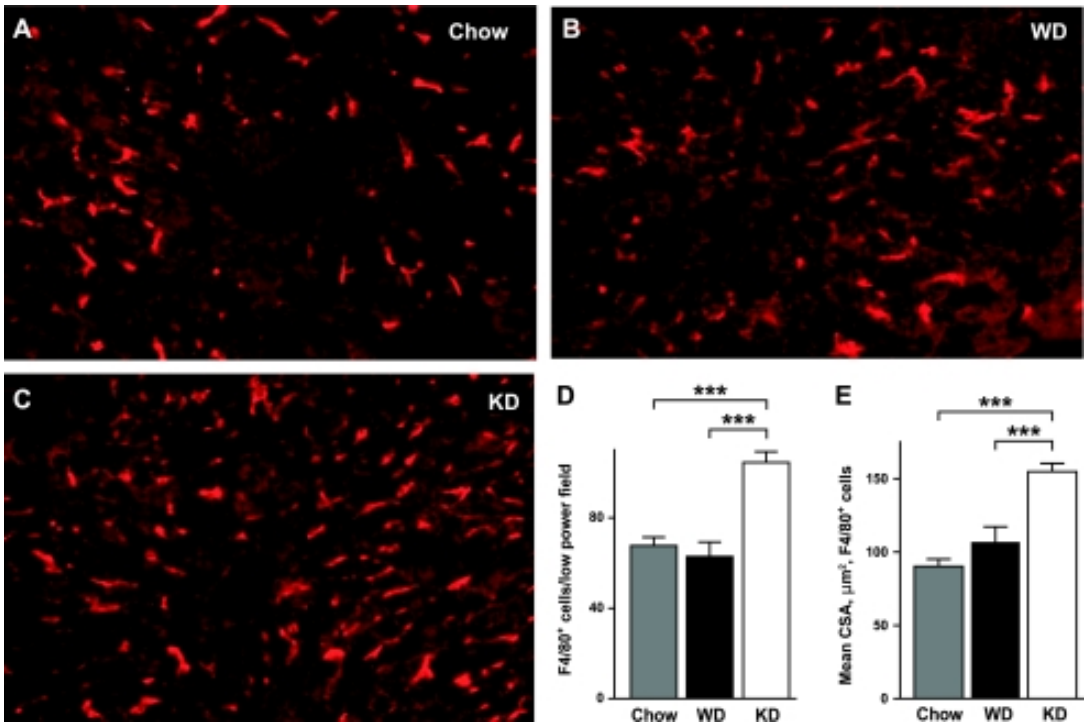
- "Acidosis may play a significant role in the mechanism of KD BMC loss. The ketone bodies are acidic, yet blood pH in children on the KD is usually normal. The serum bicarbonate is often lower than normal, indicating an insufficient production or increased need of the bicarbonate ion associated with the KD. The acidic environment of the KD may be preventing the normal accumulation of BMC."
- Acidosis may also have an effect on linear growth, and growth faltering was reported with both AEDs that cause acidosis and with the KD. In this study, linear growth velocity was particularly affected, which is primarily regulated by growth hormone and insulin-like growth factor I. Insulin-like growth factor I is also instrumental in bone formation and may be suppressed by a KD. Thus, the failure to accrue bone mineral on the KD is likely multi-factorial and may include direct or indirect efforts of disruption of the growth hormone axis."

Brinkworth, et al., 2009: "Long-term Effects of a Very Low-Carbohydrate Diet and a Low-Fat Diet on Mood and Cognitive Function"

Findings: 118 adults eating either ketogenic or isocaloric conventional diet; mood improved only initially and then rebounded towards baseline for low-carb group; sustained improvements for low-fat group
Mechanism: "Mood among long-term consumers of LC diets may also be negatively affected by changes in serotogenic expression and neurotrophic factors"

Garbow, et al., 2011: "Hepatic steatosis, inflammation, and ER stress in mice maintained long term on a very low-carbohydrate ketogenic diet"

Findings: Healthy WT mice on ketogenic diet for 12 weeks; increased macrophage markers
Mechanism: Note NAFLD found to be due to synergistic negative impact of choline deficiency and low protein (not high fat) in subsequent paper (Schugar, et al, 2013)



Kim, et al., 2012: "Inflammation-mediated memory dysfunction and effects of a ketogenic diet in a murine model of multiple sclerosis"

Findings: Mouse model of MS (EAE), showed reduced inflammation reduced CD4+ cells [i.e., Th1, Th2], reduced macrophages, increase in Treg in brain, but no change in inflammatory cell counts in periphery)

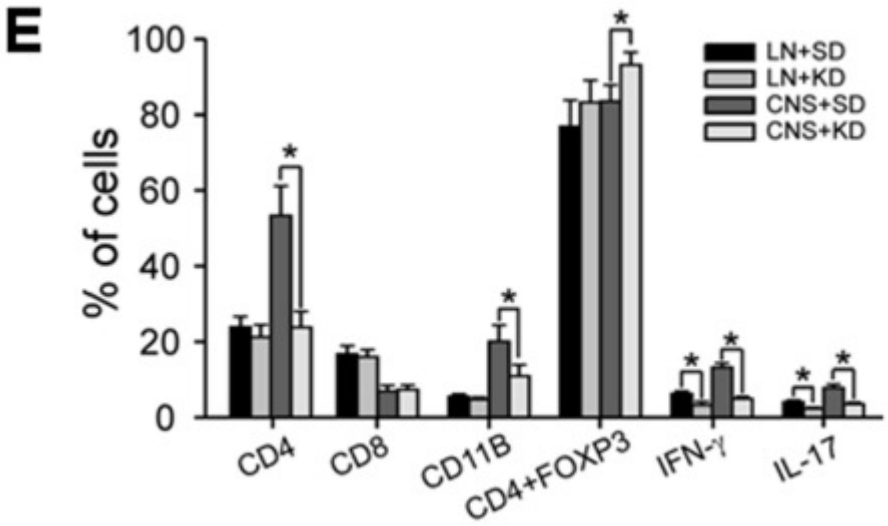
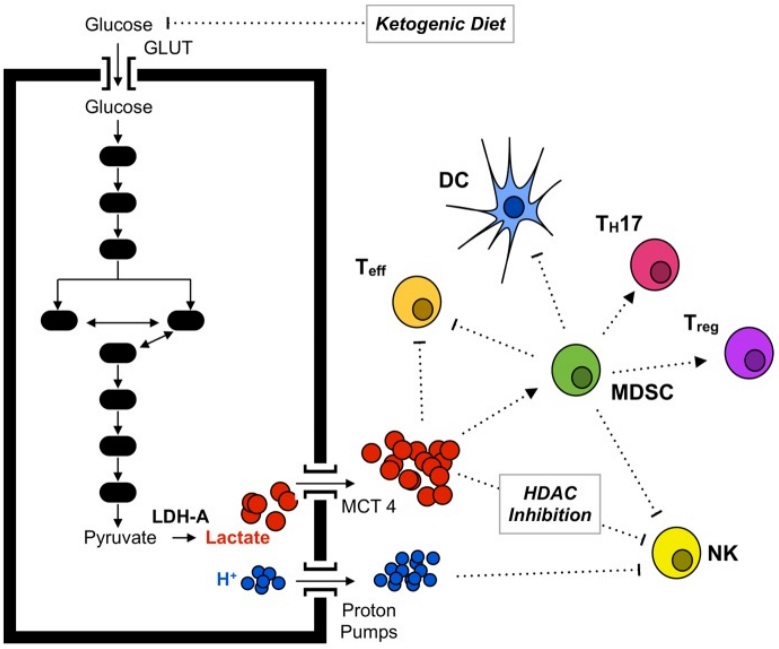


Figure 1: LN=lymph node, CNS=central nervous system

Husain, et al., 2013: "Tumor-derived lactate and myeloid-derived suppressor cells: Linking metabolism to cancer immunology"

Findings: Lactate from cancer cells stimulates production of stimulate the generation of MDSC, which inhibit T-cell activation, suppress natural killer (NK)-cell cytotoxicity, favoring the development of Tregs and preventing the maturation of DCs

Mechanism: Ketogenic diets can deplete tumor-bearing animals from MDSCs and regulatory T cells, thereby improving their immunological profile.



David, et al., 2014: "Diet rapidly and reproducibly alters the human gut microbiome"

Findings: 10 adults eating "plant-based diet" based on grains, legumes, fruits, and vegetables or an "animal-based diet" (ketogenic levels of fat intake) based on meats, eggs, and cheese; ketogenic diet increased bacteroidetes, decreased firmicutes (on the surface, this sounds good; see Kallus SJ and Brandt LJ. The intestinal microbiota and obesity. J Clin Gastroenterol. 2012 Jan;46(1):16-24. doi: 10.1097/MCG.0b013e31823711fd.)

- Decrease in beta-diversity (diversity is the #1 most important aspect of the gut microbiome; see Jason M. Norman, Scott A. Handley, Herbert W. Virgin. **Kingdom-agnostic Metagenomics and the Importance of Complete Characterization of Enteric Microbial Communities**. *Gastroenterology*, 2014; DOI: 10.1053/j.gastro.2014.02.001)
- Increase in Bilophila wadsworthia (see Baron EJ, Bilophila wadsworthia: a unique Gram-negative anaerobic rod. Anaerobe. 1997 Apr-Jun;3(2-3):83-6.)
- Decrease in Prevotella genus (makes up 53% of bacteroidetes in rural African children, see De Filippo, C.; Cavalieri, D.; Di Paola, M.; Ramazzotti, M.; Poullet, J. B.; Massart, S.; Collini, S.; Pieraccini, G.; Lionetti, P. (2010). "Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa". *Proceedings of the National Academy of Sciences* **107** (33): 14691–6. doi:10.1073/pnas.1005963107. PMC 2930426. PMID 20679230.) Prevotella associated with longevity, see Park SH, et al., Comparative analysis of gut microbiota in elderly people of urbanized towns and longevity villages. BMC Microbiol. 2015 Feb 26;15(1):49. doi: 10.1186/s12866-015-0386-8.
- Increase in bacteroides genus (some are good, some are pathogenic, see Wexler HM. Bacteroides: the good, the bad, and the nitty-gritty. Clin Microbiol Rev. 2007 Oct;20(4):593-621.)

	Meal	Food item	
Plant-based diet	Breakfast	Granola cereal	
	Lunch	Jasmine rice	Steamed lentils
		Fresh onions	Chili powder
		Fresh tomato	Cumin
		Fresh butternut squash	Coriander seed
		Fresh garlic	Vegetable oil
		Frozen peas	Salt
	Dinner	Jasmine rice	Frozen spinach
		Fresh cauliflower	Fresh tomato
		Fresh carrots	Vegetable oil
		Fresh onions	Mustard oil
		Fresh green chile	Chili powder
		Fresh garlic	Cumin
		Steamed lentils	Coriander seed
	Snacks	Fresh banana	Fresh papayas
		Fresh mangoes	Banana chips
Animal-based diet	Breakfast	Cooked bacon	Brewed coffee
		Scrambled eggs	Half & half cream
	Lunch	Pork spare ribs	
		Beef brisket	
	Dinner meats	Salami	
		Prosciutto	
	Dinner cheeses	Blue	Caerphilly
		Cheddar	Camembert
	Snacks	Salami	Pork rinds
		Mozarella string cheese	

Studies of Inuit Eskimos and Lack of Ketosis

Summary of key points:

- Inuit diet was too high in combined protein + carbohydrate to produce ketosis in most human beings
- Stefansson significantly modified the diet he learned from the Eskimos during his year-long meat experiment (zero carbohydrate instead of 30 – 50g from animal glycogen; ≈20% protein instead of 30 – 35% or more; no fresh raw meat high in glycogen); he was not eating an actual Inuit diet
- The majority of Inuit are either homozygous or heterozygous for CPT-1A mutation that makes nutritional ketosis nearly impossible

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Eskimo diet too high in protein and carbohydrate to induce ketosis; no measured evidence of ketosis; high glucose tolerance:

Heinbecker, 1928: "Studies on the Metabolism of Eskimos"

- Breakdown of traditional Eskimo diet:
  - 280g/day of protein
  - 135g/day of fat
  - 54g/day of carbohydrate ("of which the bulk is derived from the glycogen of the meat eaten")
- "The metabolism of the foodstuffs contained in the Eskimo dietary would not be expected to cause ketosis, because the calculated antiketogenic effect of the large protein ingestion was somewhat more than enough to offset the ketogenic effect of fat plus protein"
- On normal diet, Eskimos showed no evidence of ketosis and had high glucose tolerance (*unlike* most modern ketogenic dieters, who fail oral glucose tolerance tests while in nutritional ketosis)

Corcoran and Rabinowitch, 1936: "A Study of the Blood Lipoids and Blood Protein in Canadian Eastern Arctic Eskimos"

- "Absence of ketosis in these natives"
- "Though the small amount of carbohydrates in the diets may be more than balanced by the potential sugar production from the large amount of protein to keep the ratio of fatty acid to glucose below the generally accepted level of ketogenesis, the respiratory quotient data suggest another mechanism also" ← (most likely the CPT-1A mutation, which had not been discovered at that time)

Ho, et al., 1972: "Alaskan Arctic Eskimo: Responses to a Customary High Fat Diet"

- Breakdown of traditional Eskimo diet:
  - Average calorie intake = 3,000 per person (2,300 – 4,500 range)
  - 50% calories from fat
  - 30 to 35% calories from protein (260g on average)
  - 15 to 20% calories from carbohydrate, mostly glycogen from meat
- "Strip paper technique" showed all measured serums were negative for ketone bodies

Eskimos prize higher-carbohydrate animal foods:

"A study of the diet and metabolism of Eskimos undertaken in 1908 on an expedition to Greenland," 1914

- "The skin of young whales is considered a special delicacy. It has been examined recently by Bertelsen and found to contain an extraordinary large proportion of glycogen"
- "The normal diet of Eskimos contains an excessive amount of animal protein (280 gr.) and much fat (135 gr.) while the quantity of carbohydrate is extremely small (54 gr. of which more than ½ is derived as glycogen from the meat eaten)."

Genetic mutation prevents ketosis:

Clemente, et al., 2014: "A Selective Sweep on a Deleterious Mutation in CPT1A in Arctic Populations"

- Mutation: CPT-1A, P479L variant
- Defect evolved in multiple unrelated populations, common denominator being cold climate and low access to carbohydrate
- Mutation places a leucine in the place of a proline in CPT-1a (major rate-limiting enzyme for long-chain fatty acid oxidation)
- Mutation is linked to failure to generate ketones in infancy; associated with extreme hypoglycemia that can potentially cause death

Greenberg, et al., 200p: "The paradox of the carnitine palmitoyltransferase type Ia P479L variant in Canadian Aboriginal populations"

- Out of 422 consecutive newborns screened, 294 were homozygous for P479L variant; 103 were heterozygous; 25 were homozygous normal
- "It is likely that the P479L variant is of ancient origin and presumably its preservation must have conveyed some advantage"

Vilhjalmur Stefansson, Bellevue experiment: not actually consuming macronutrient ratios of the Eskimos

McClellan and DuBois, 1930: "Prolonged Meat Diets with a Study of Kidney Function and Ketosis"

- First two days of diet: Stefansson approximated diet of the Eskimos (as reported by Krogh and Krogh), but ate only at 1/3 as much carbohydrate; protein intake was 45 percent of calories
- "The intestinal disturbance began on the 3rd day of this diet"—subsequently, Stefansson switched to 80% calories from fat and 20% from protein; in two days his intestinal symptoms vanished without medication
- For the rest of experiment, protein calories didn't exceed 25% for more than one day at a time

Tolstoi, 1929: "The Effect Of An Exclusive Meat Diet Lasting One Year On The Carbohydrate Tolerance Of Two Normal Men"

- After diet, Stefansson and Anderson's failed to exhibit the normal glucose tolerance seen in Eskimos on their traditional diet