

Inflammation, Nutritional Ketosis, and Metabolic Disease

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DISCLOSURES

<u>Commercial Interest</u>	<u>What Received</u>	<u>Role</u>
Virta Health Corp	Ownership Interest	Chief Medical Officer Co-founder
Beyond Obesity, LLC	Book Royalties	Author
Atkins Nutritionals, Inc	Honorarium	Science Advisor

The New Science of BOHB

Reduced oxidative stress reduces aging and inflammation

Suppression of Oxidative Stress by β -Hydroxybutyrate, an Endogenous Histone Deacetylase Inhibitor

Tadahiro Shimazu^{1,2}, Matthew D. Hirschey^{1,2}, John Newman^{1,2}, Wenjuan He^{1,2}, Kotaro Shirakawa^{1,2}, Natacha Le Moan³, ...

+ See all authors and affiliations

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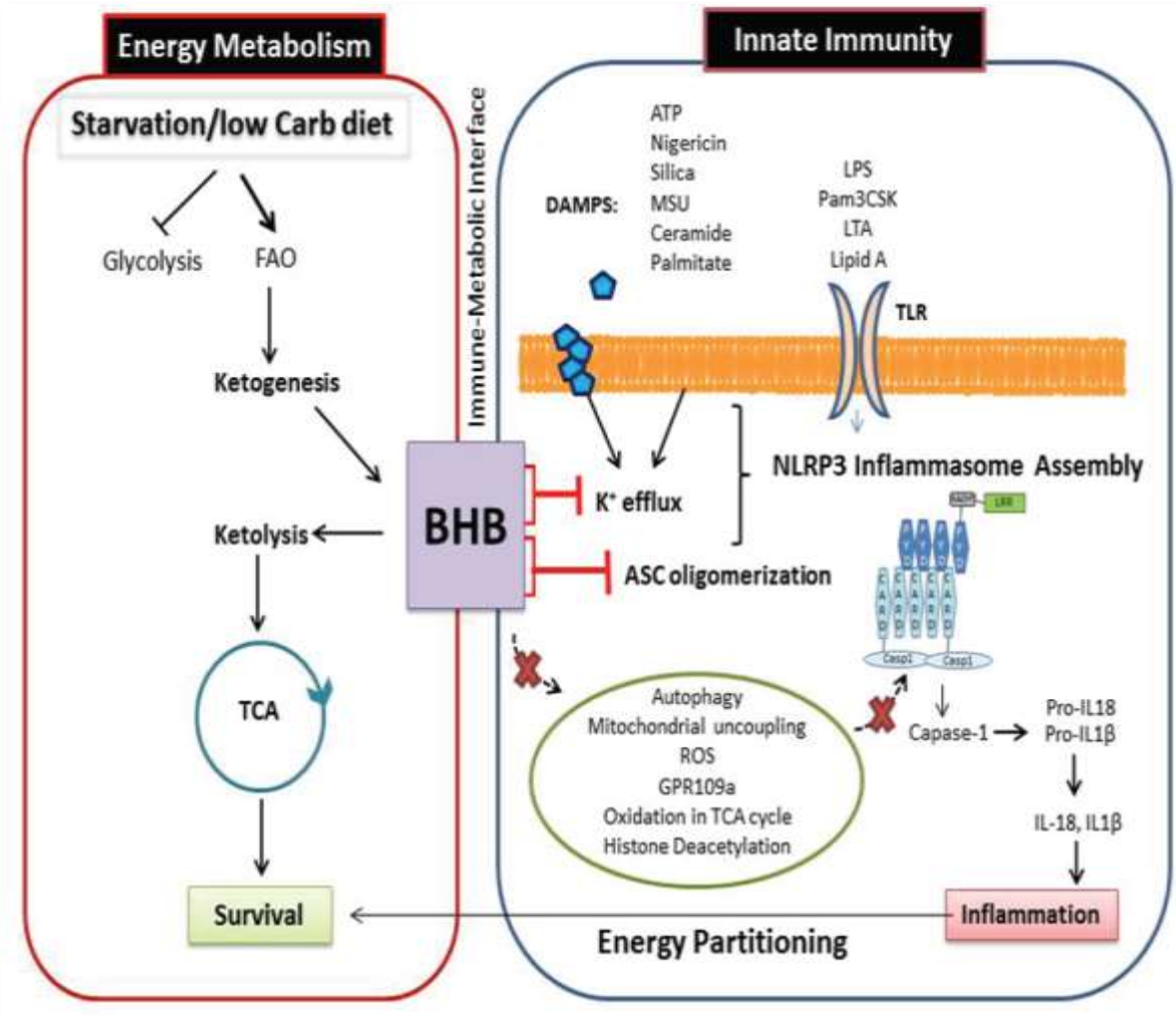
Invited Review

β -hydroxybutyrate: Much more than a metabolite

John C. Newman^{a, b}, Eric Verdin^b  

Possible direct effects on insulin resistance

β OHB Inhibits Inflammatory Gene Expression



- β OHB does not just reduce isoprostane production (prostaglandin-like compounds formed by ROS-peroxidation of essential fatty acids like ARA)
- It intervenes at the regulatory level by blocking NLRP3 inflammasome-mediated inflammatory disease

Inflammation and Type 2 Diabetes

Type 2 diabetes as an inflammatory disease

Marc Y. Donath and Steven E. Shoelson†*

www.nature.com/reviews

Immunity
FEBRUARY 2011 | VOLUME 11

The Journal of Clinical Investigation

REVIEW SERIES: METABOLISM AND INFLAMMATION

Series Editors: Alan R. Saltiel and Jerrold M. Olefsky

Inflammatory mechanisms linking obesity and metabolic disease

Alan R. Saltiel and Jerrold M. Olefsky

jci.org Volume 127 Number 1 January 2017

Department of Medicine, UCSD, La Jolla, California, USA.

White Blood Cell Count and Coronary Risk

Early associations between CVD and inflammation

**Fibrinogen, viscosity, and white blood cell count are major risk factors for ischemic heart disease.
The Caerphilly and Speedwell collaborative heart disease studies.**

J W Yarnell, I A Baker, P M Sweetnam, D Bainton, J R O'Brien, P J Whitehead, P C Elwood

Circulation. 1991 ;83:836-844

- 4860 healthy men followed for 3-5 years.
- The top quintile vs bottom quintile for WBC count had a 3-fold increased risk of incident ischemic heart disease.

White blood cell count and cardiovascular disease: insights from the Framingham Study

WB Kannel, K. Anderson, P W F Wilson.

JAMA 1992; 267:1253-1256.

- 1393 men and 1401 women without heart disease followed for 12 years
- For men and women with baseline WBC count in the normal range, each added 1.0×10^9 increased CVD risk by 32% and 17% respectively.
- This was partially explained by smoking, but independent of total and LDL-cholesterol.
- For non-smoking men with WBC > 6.0, ischemic heart disease risk was 2.1 times greater than those with WBC < 6.0

Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein

Ridker PM, Danielson E, Fonseca FA, et al.. *N Engl J Med* 2008, 359:2195-2207.

- 17,802 healthy subjects with LDL-C <130 and CRP > 2.0 randomized to 20 mg/d rosuvastatin or placebo.
- Primary endpoint was first major cardiovascular event
- Study halted after median of 1.9 years of follow-up due to hazard ratio of 0.56, P<0.00001.
- LDL-C reduced by 50%
- **CRP reduced by 37%**

Bottom line: Highly significant primary prevention outcome, but unable to assign clear causality to either LDL or CRP reduction.

Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease

Paul M Ridker, Brendan M. Everett, et al., for the CANTOS Trial.
N Engl J Med 2017; 377:1119-1131

- 10,061 S/P MI and elevated CRP were randomized to receive 1 of 3 doses of this anti-IL-1B monoclonal antibody or placebo for 4 years.
- Canakinumab did not reduce lipid levels from baseline.
- **CRP was reduced by 26 to 41%** in a dose-dependent manner.
- **Relative risk for primary cardiovascular endpoints were reduced** at all doses from 0.93 to 0.80 compared to placebo, but significantly only in the intermediate dose group ($P < 0.005$)
- **Canakinumab use was associated with an increase in fatal sepsis**, such that there was no significant reduction in overall mortality.

Bottom Line: this highly focused anti-inflammatory pharmaceutical can reduce coronary mortality associated with a reduction in CRP, but the fatal side effects cancel any net therapeutic benefit.

Can Nutrients Modulate Inflammation?

Many nutrients are weak inflammation antagonists

- Fish oil or DHA
- Gamma-linolenic acid
- Resveratrol

Gamma-tocopherol is a potent anti-inflammatory

- Alpha and gamma tocopherol metabolism in healthy subjects and patients with end-stage renal disease. J Himmelfarb, E McMonagle, E Zaltas, S Bobzin, S Boddupalli, S Phinney, G Miller. *Kidney Internat.* 2003; 64:978–991
- γ -Tocopherol, but not α -tocopherol, decreases pro-inflammatory eicosanoids and inflammation damage in rats. Q Jiang, BN Ames. *The FASEB Journal*, 2003; <https://doi.org/10.1096/fj.02-0877com>

Gamma-tocopherol + DHA + Flavenoids can reduce CRP by 50% in 2 weeks

- Formulations and methods for treatment or amelioration of inflammatory conditions. US Patent Application 20030144219A1. Inventors: Dreon and Phinney for Galileo Labs. (Abandoned).
- Tocopherol enriched compositions and amelioration of inflammatory symptoms. US Patent 7119117B2. Inventors: Beinlich, Boddupalli, Dreon, Miller, Phinney for Galileo Labs. **Current Assignee: Johnson and Johnson Consumer Companies** ('locked up' until 2021)

LFD versus LCD for Metabolic Syndrome

Lipids

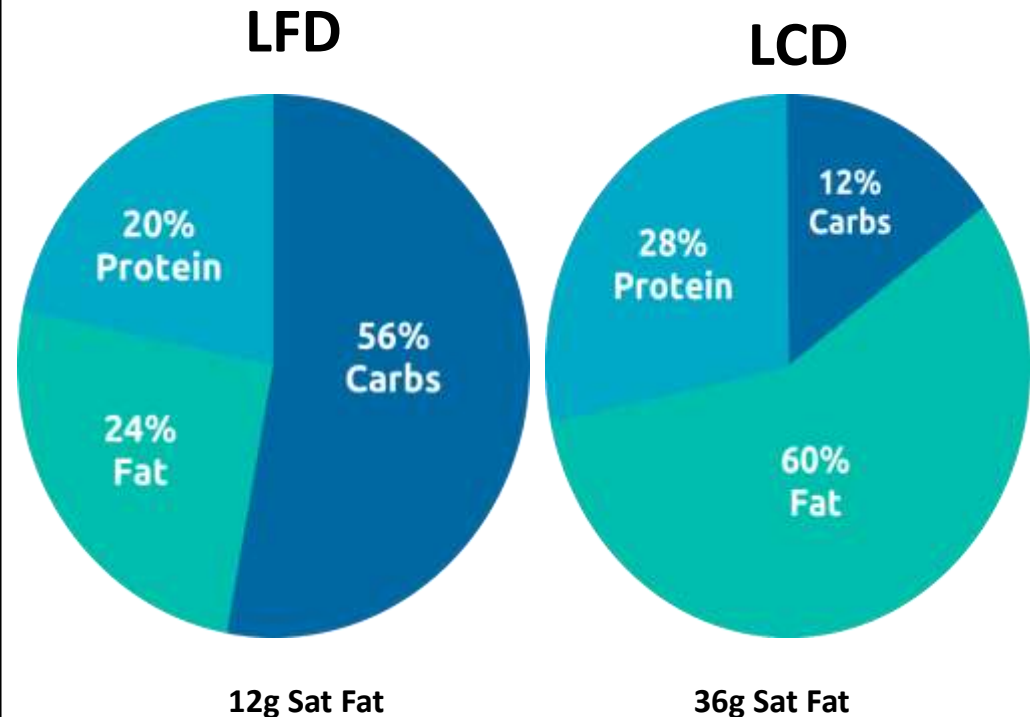
N = 40

Demographics:

- 40 overweight subjects with atherogenic dyslipidemia
- Age: 18 – 55 years
- BMI > 25 kg/m²

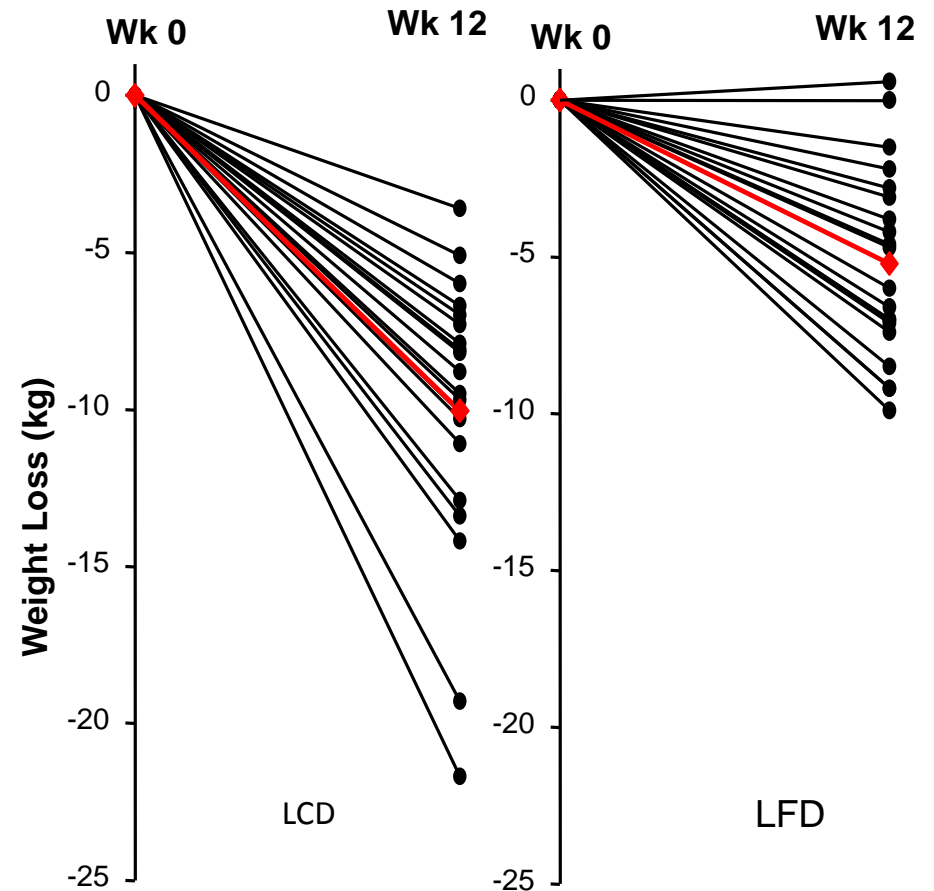
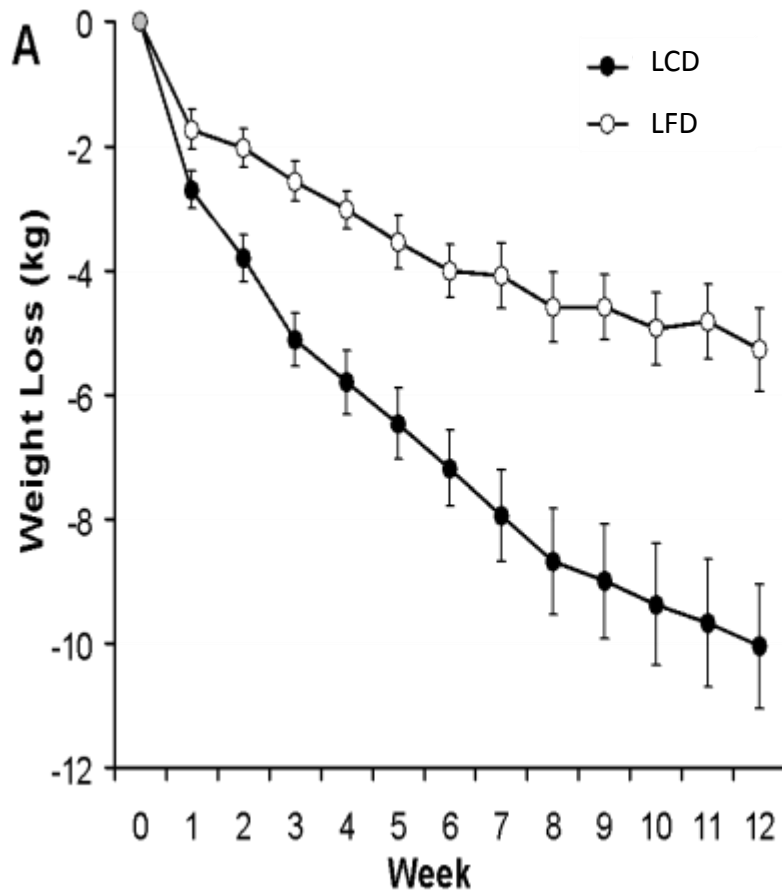
Method:

- Outpatient for 12 weeks
- Two randomly assigned groups:
 - LCD: eaten to satiety (reported 1500 kcal); 12% carb, 59% fat, 28% protein
 - Hypocaloric LFD: 1,500 kcal, 56% carb; 24% fat; 20% protein



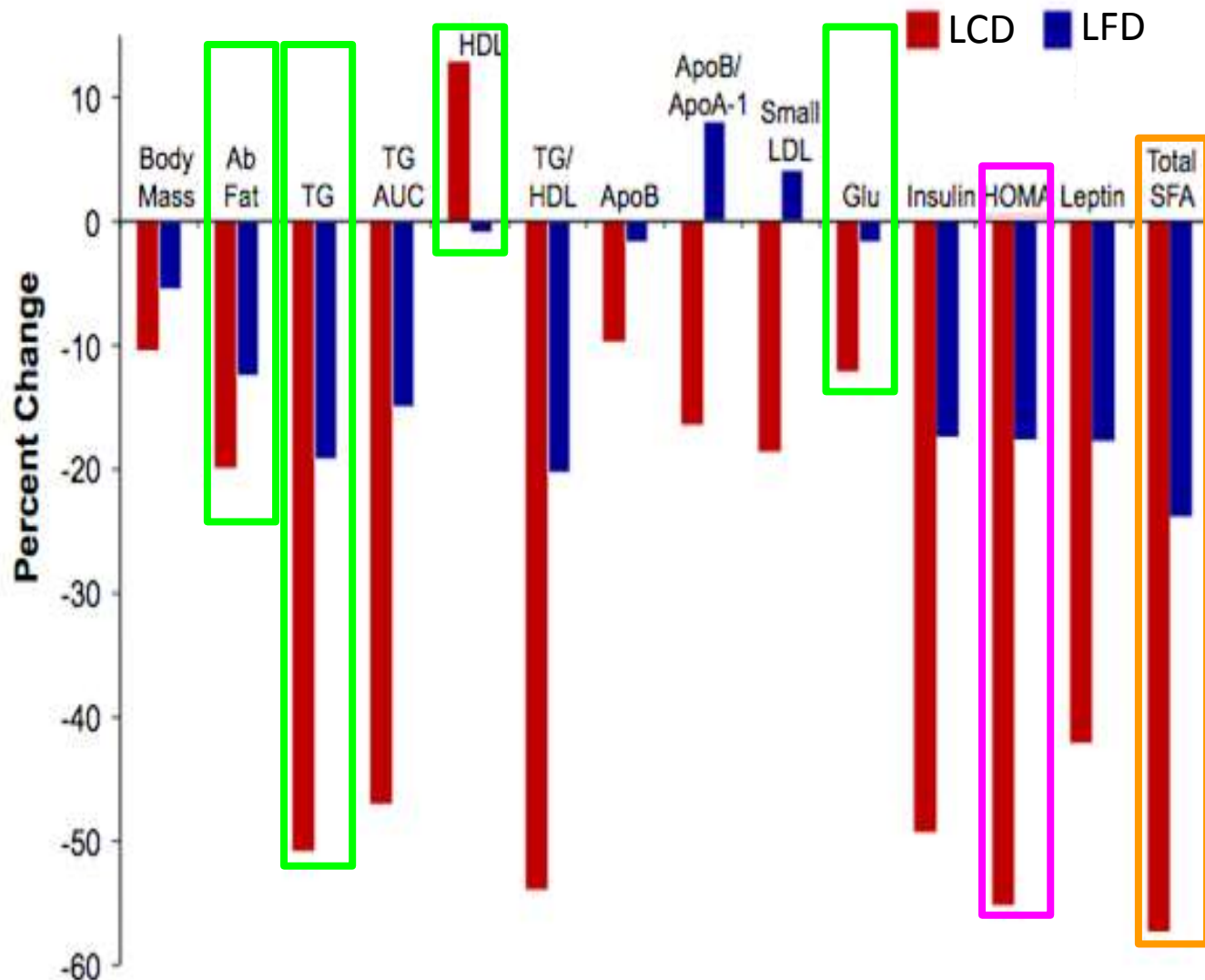
Source: Forsythe et al.; “Carbohydrate Restriction has a More Favorable Impact on the Metabolic Syndrome than a Low Fat Diet”; Lipids (2009)

Wt Loss: LFD versus LCD for Metabolic Syndrome



- While both groups continue weight loss at 12-weeks, **LCD weight loss significantly greater**

Results: LFD versus LCD for Metabolic Syndrome

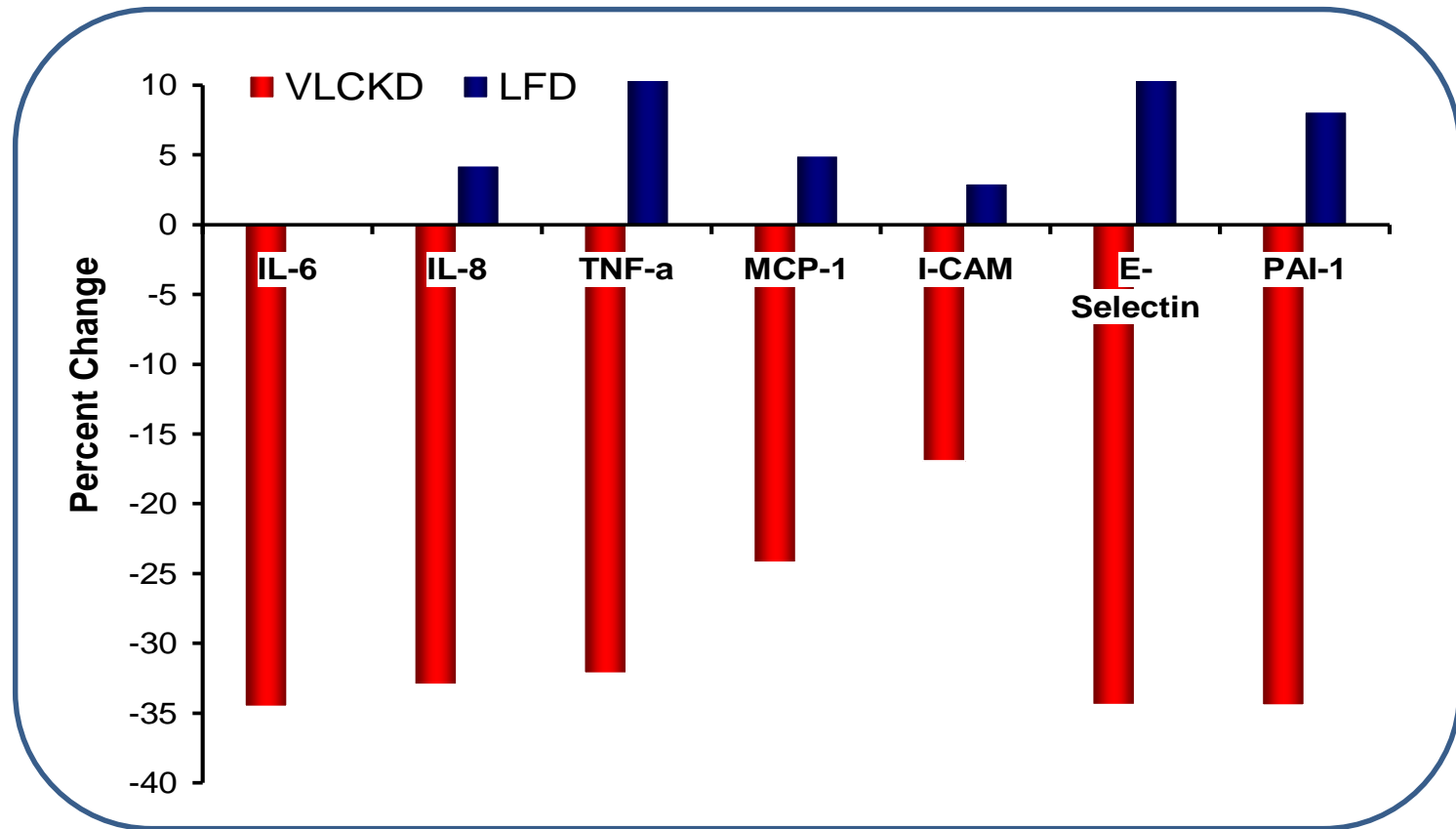


- All the **markers of MetS improved**, significantly better in LC than LF
 - Except BP (not shown)
- **Marker of insulin resistance (HOMA-IR) improved** dramatically for LC than LF
- **Total SFA** was dramatically lower in LC than LF in serum, even though dietary intake was 3x higher
 - Likely because patients are so much better at oxidizing it

Source: Forsythe et al.; "Carbohydrate Restriction has a More Favorable Impact on the Metabolic Syndrome than a Low Fat Diet"; Lipids (2009)

A ketogenic diet has potent anti-inflammatory effects

LCD vs LFD: 7 of 14 inflammation biomarkers significantly reduced



THE IUH CLINICAL TRIAL
Principal Investigator
Dr. Sarah Hallberg

Our Patients

N = 262 living with T2D

Location: Central
Indiana

Average Age: 54

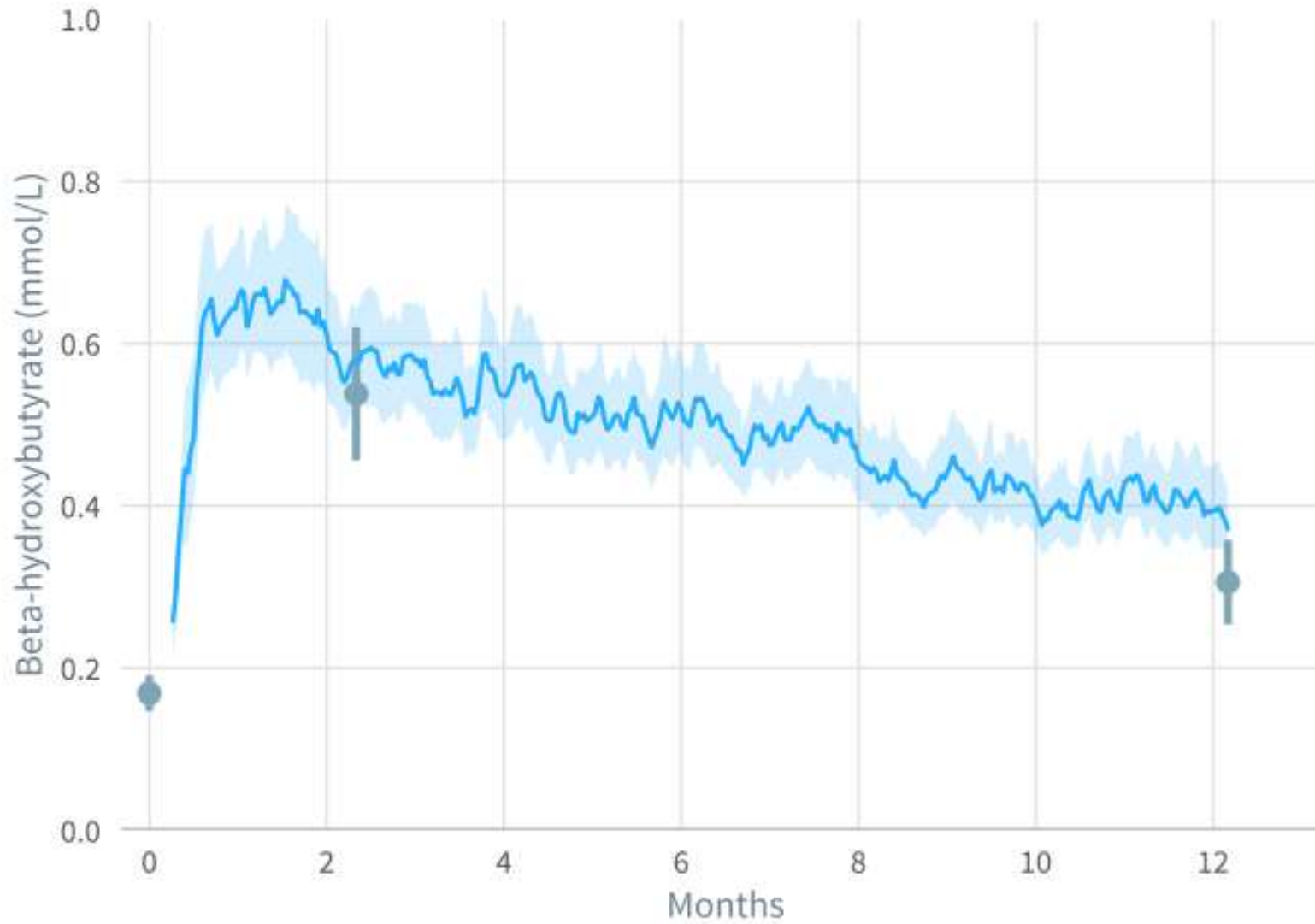
Average BMI: 41

Average Weight: 257 lbs

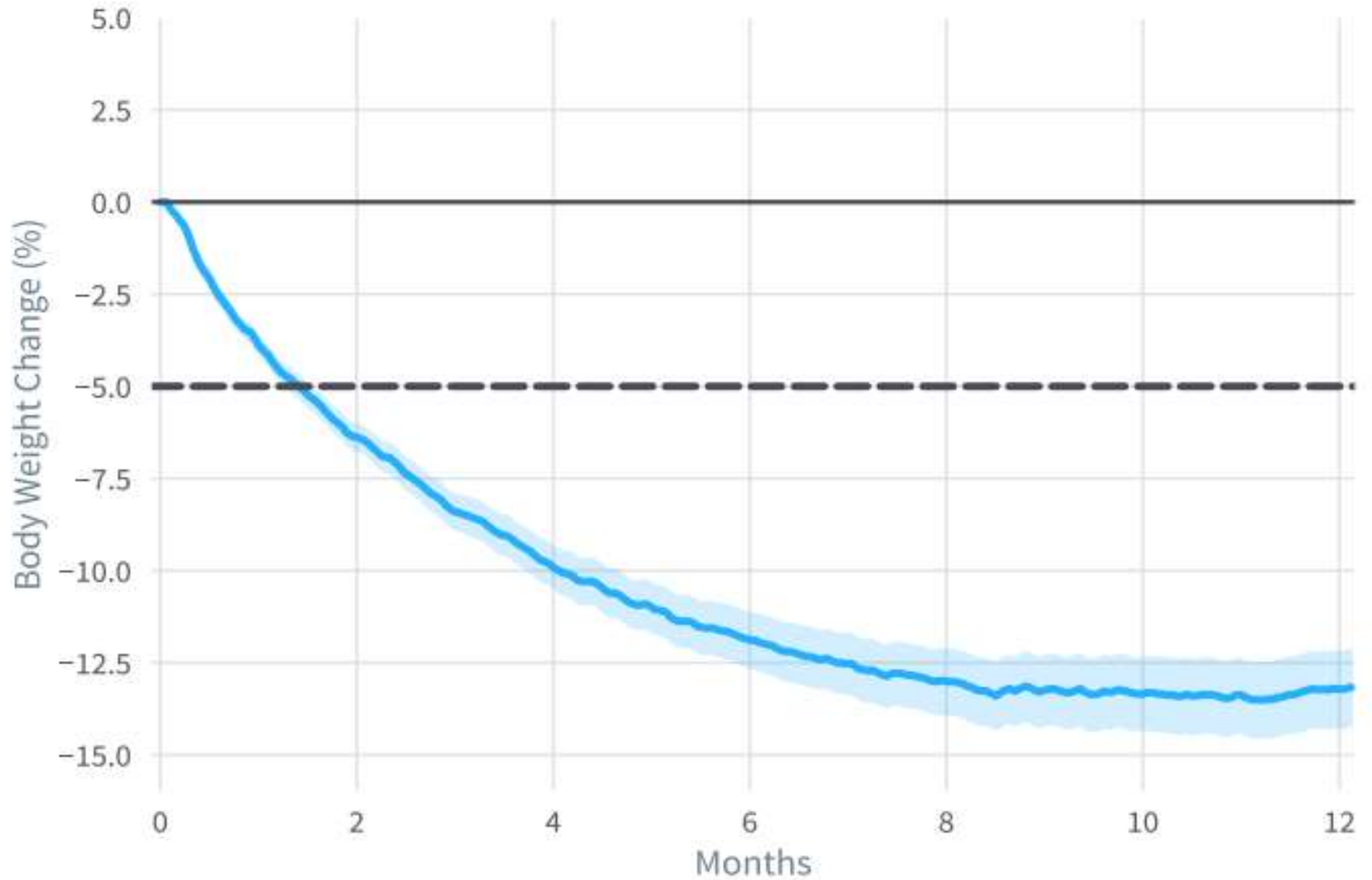
67% female



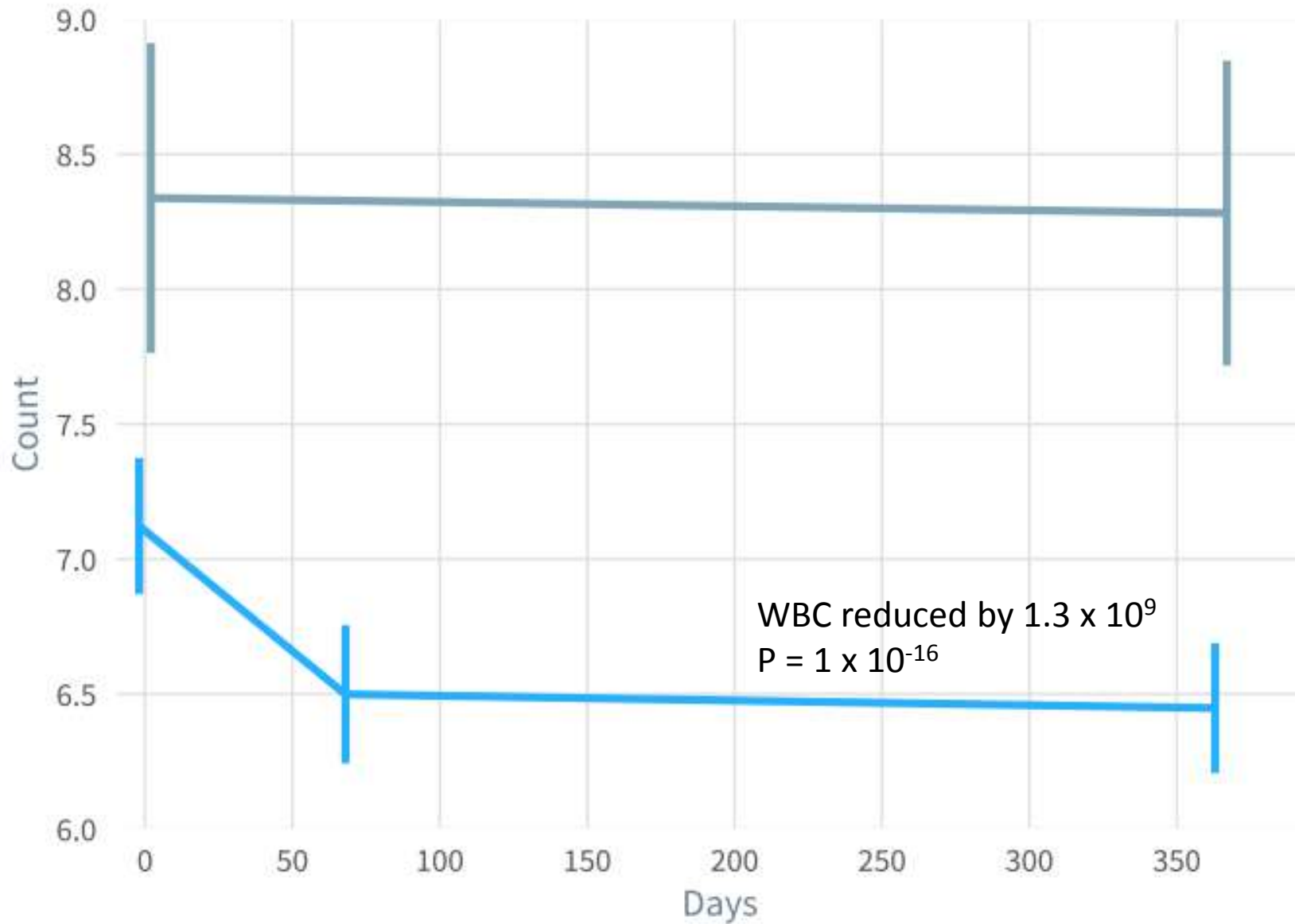
Beta-hydroxybutyrate Continuous Care



Weight Change Continuous Care



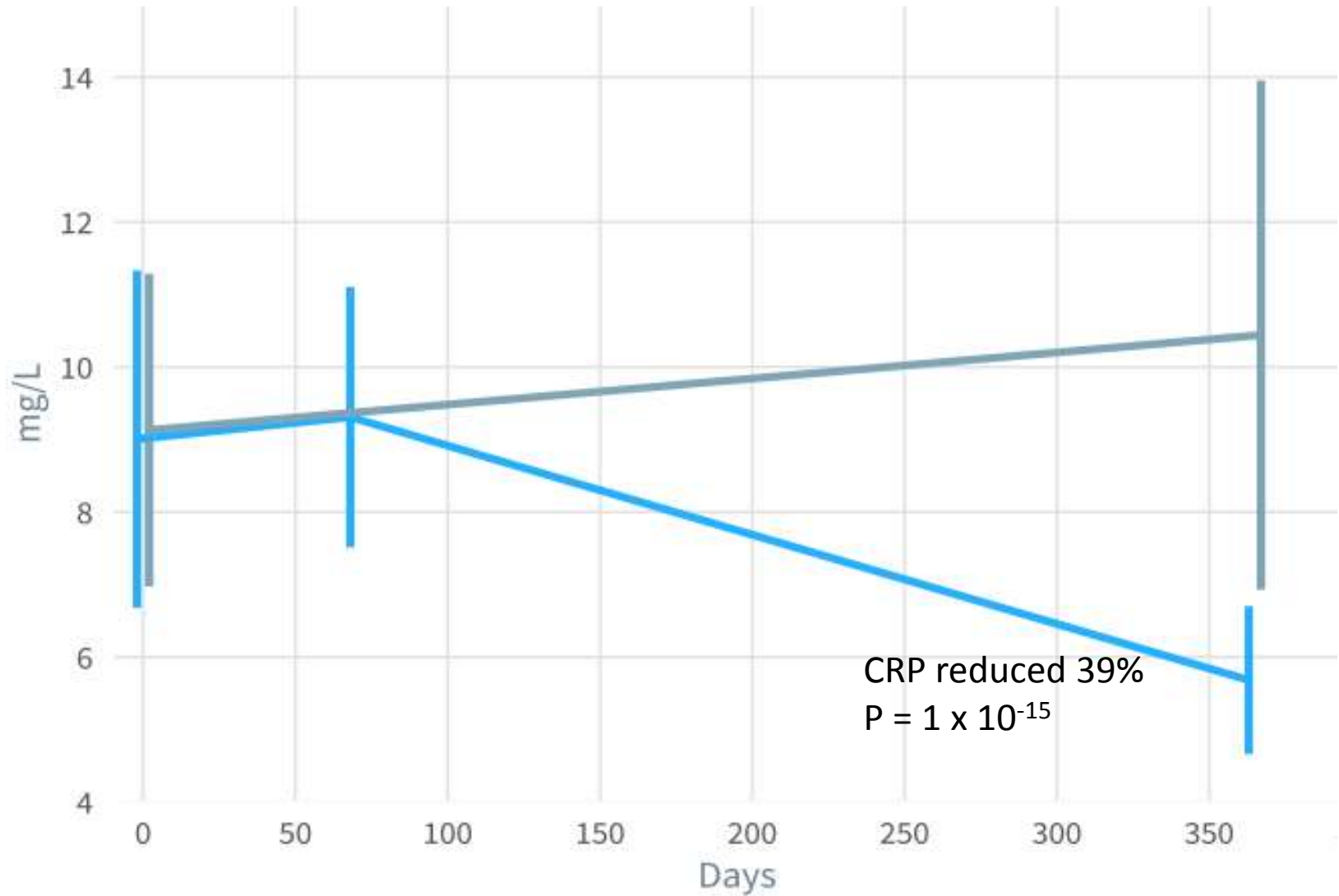
White Blood Cell Count



McKenzie et al. JMIR Diabetes. 2017;2(1):e5 DOI: [10.2196/diabetes.6981](https://doi.org/10.2196/diabetes.6981)

Hallberg et al. Diabetes Therapy. 2018. <https://doi.org/10.1007/s13300-018-0373-9>

C-Reactive Protein



McKenzie et al. JMIR Diabetes. 2017;2(1):e5 DOI: [10.2196/diabetes.6981](https://doi.org/10.2196/diabetes.6981)

Hallberg et al. Diabetes Therapy. 2018. <https://doi.org/10.1007/s13300-018-0373-9>

Conclusions

What's there to say?

- There is no drug approved for chronic use that can deliver these potent anti-inflammatory benefits without side effects.
- The gamma-tocopherol DHA formulation is potentially available in a few years.
- But no one has a patent on a well-formulated ketogenic diet. Given adequate instruction and support, pretty much anyone can do it and a majority of people will likely benefit.