

# MANAGING INSULIN RESISTANCE (CARBOHYDRATE INTOLERANCE) WITH A KETOGENIC DIET

Jan 8, 2018



THE OHIO STATE UNIVERSITY

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***Jeff S. Volek, PhD, RD***

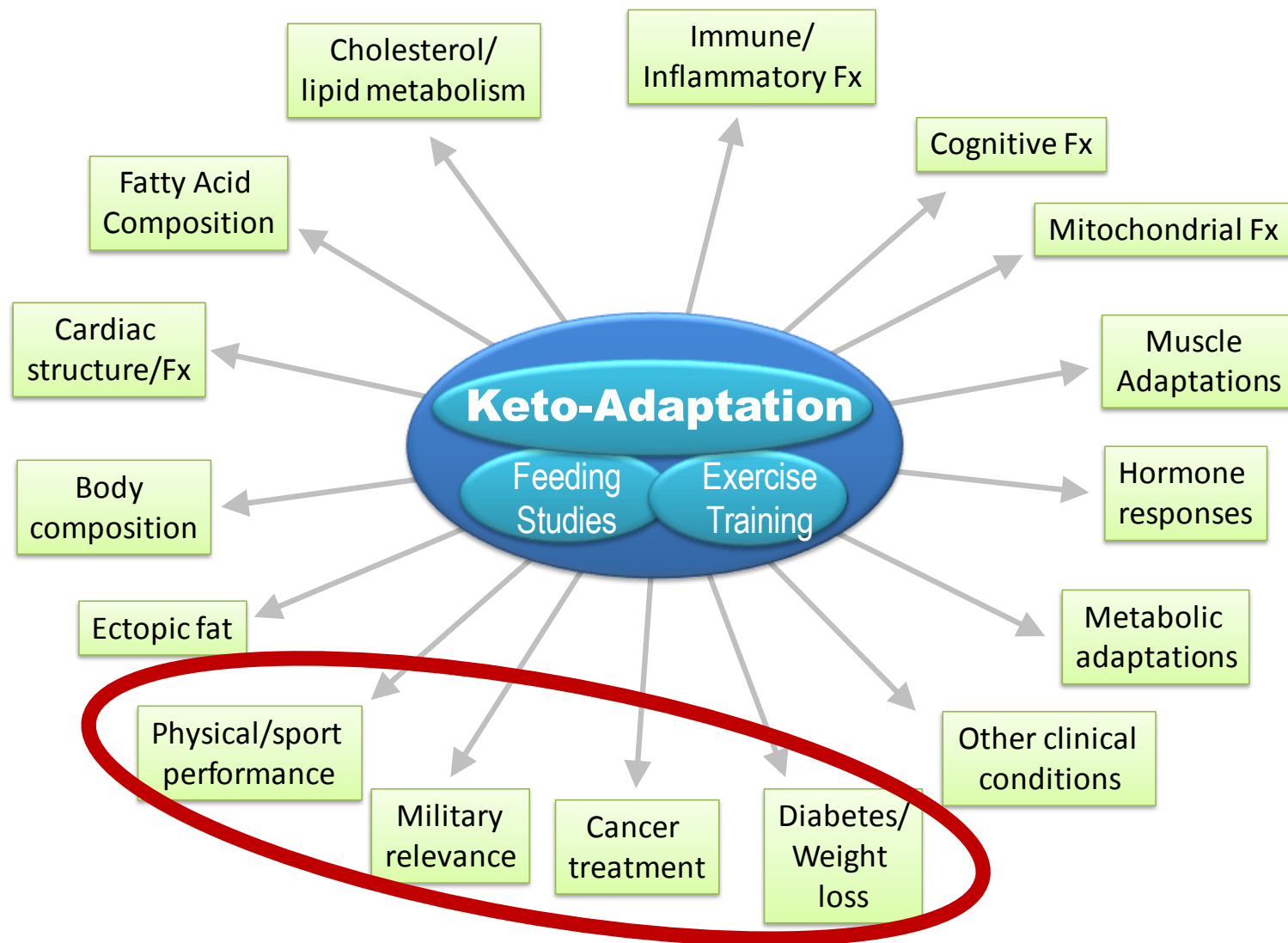
Professor

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Columbus, OH 43210

volek.1@osu.edu

# What my team does at OSU



FOR TODAY

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## **Obesity & diabetes epidemics**

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Ketones and keto-adaptation defined

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Keto-adaptation reverses prediabetes & diabetes

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Beyond obesity & diabetes

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# Obesity & Diabetes Epidemic

*Scientific consensus: diabetes is a chronic irreversible disease*

NATIONAL CENTER FOR HEALTH STATISTICS

**Health E-Stats**

JULY  
2016

Prevalence of Overweight, Obesity, and Extreme Obesity  
Among Adults Aged 20 and Over: United States, 1960–1962  
Through 2013–2014

**72%**

U.S. Adults  
overweight or  
obese

**52%**

U.S. adults  
prediabetes or  
diabetes

**25%**

U.S. adults >65 y  
w/ diabetes

Research

**Original Investigation**

**Prevalence of and Trends in Diabetes Among Adults  
in the United States, 1988-2012**

Andy Menke, PhD; Sarah Casagrande, PhD; Linda Geiss, MA; Catherine C. Cowie, PhD


# Diabetes Pandemic

## Global diabetes jumped 40% in the last two years, report says

By **Jade Scipioni** | Published June 19, 2017 | **Health Care** | **FOXBusiness**

**Across the globe, diabetes has the potential to overwhelm healthcare systems and wreck economies. Yet the disease is largely preventable and controllable.**

**aetna**



2017: Volume IV

**Diabetes:**  
The world's weightiest problem

**Dr. Stella George**, Senior Medical Director, Aetna International  
**Dr. Mitesh Patel**, Medical Director, Aetna International  
**Dr. Lori Stetz**, Senior Medical Director, Aetna International

[aetnainternational.com](http://aetnainternational.com)

# THE STAGGERING COSTS OF DIABETES IN AMERICA

Nearly

**30 million**

Americans have diabetes.

**\$1 in \$3**

Medicare dollars  
is spent caring for  
people with diabetes.

Diabetes and prediabetes cost America

**\$322 billion**

per year.

**86 million**

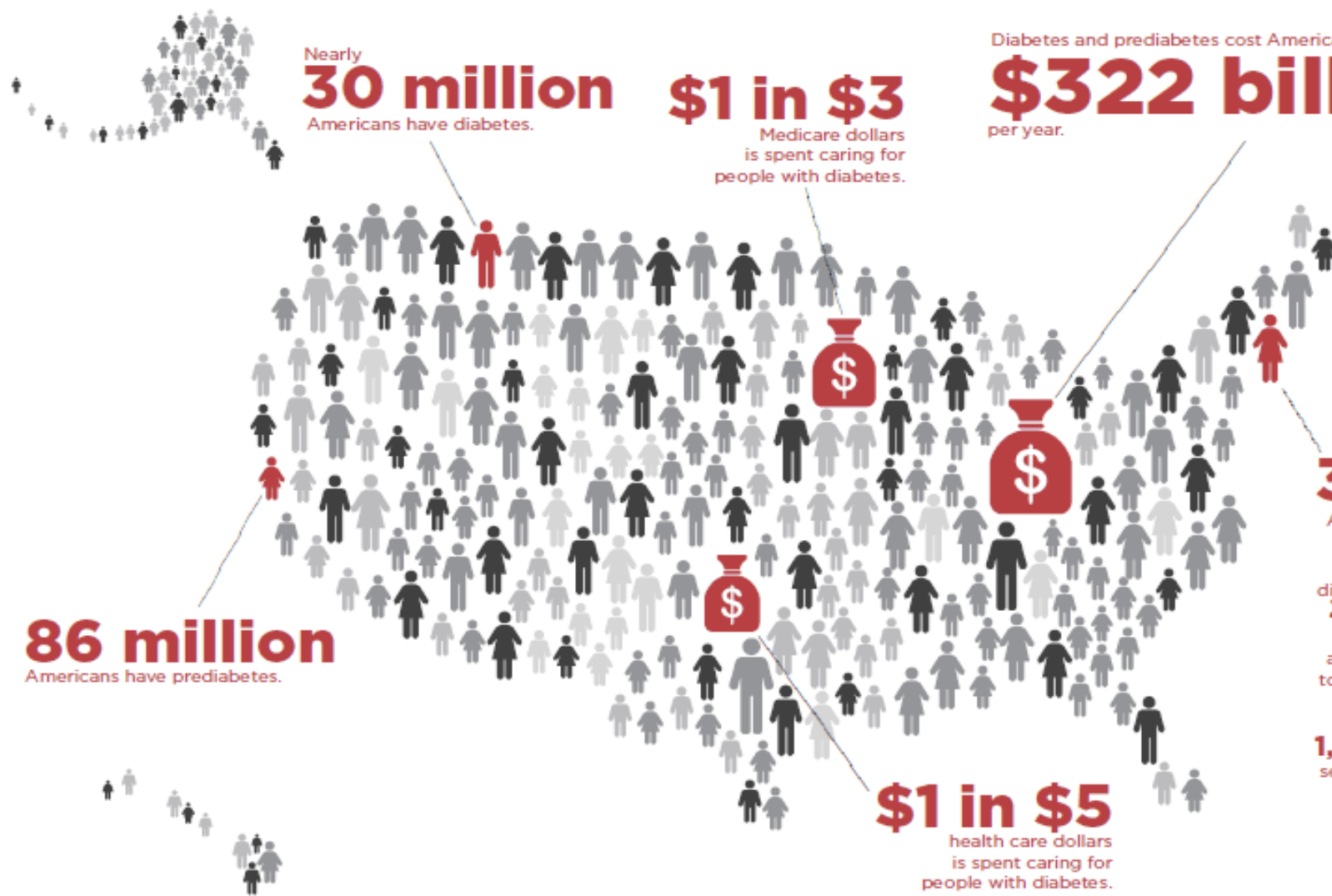
Americans have prediabetes.

Today,  
**3,835**

Americans will be  
diagnosed with  
diabetes. Today,  
diabetes will cause  
**200** Americans  
to undergo an  
amputation, **136**  
to enter end-stage  
kidney disease  
treatment and  
**1,795** to develop  
severe retinopathy  
that can lead to  
vision loss and  
blindness.

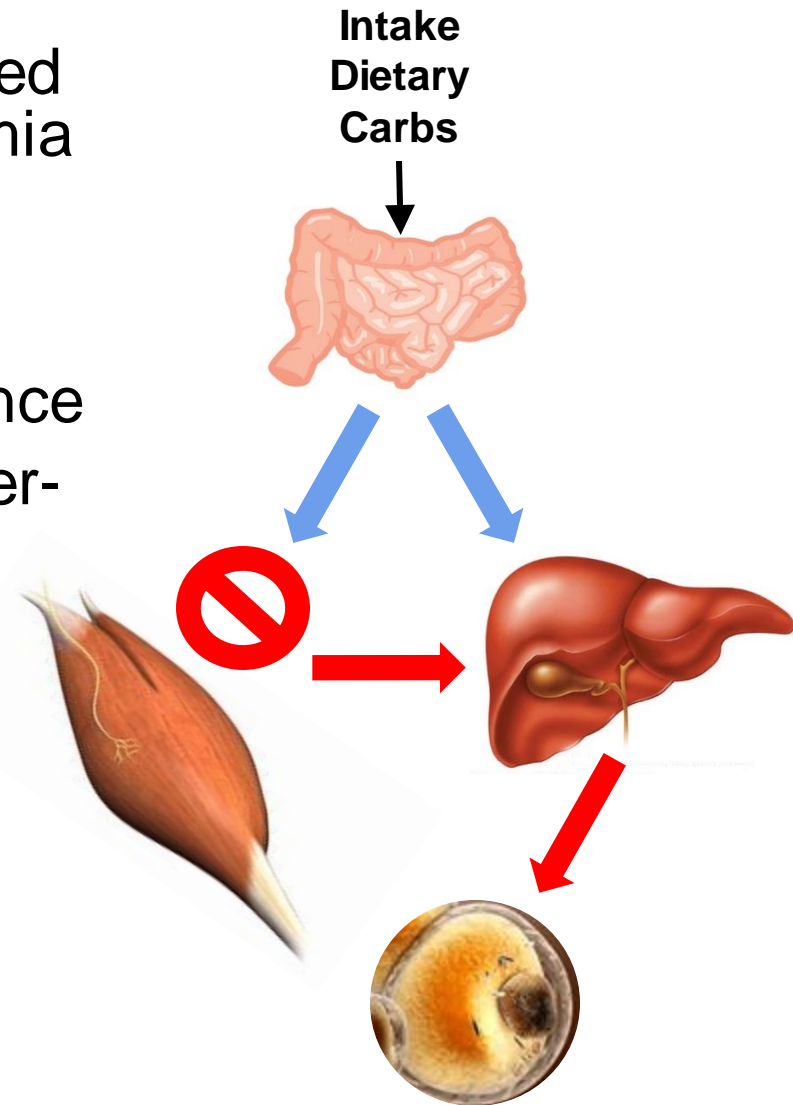
**\$1 in \$5**

health care dollars  
is spent caring for  
people with diabetes.



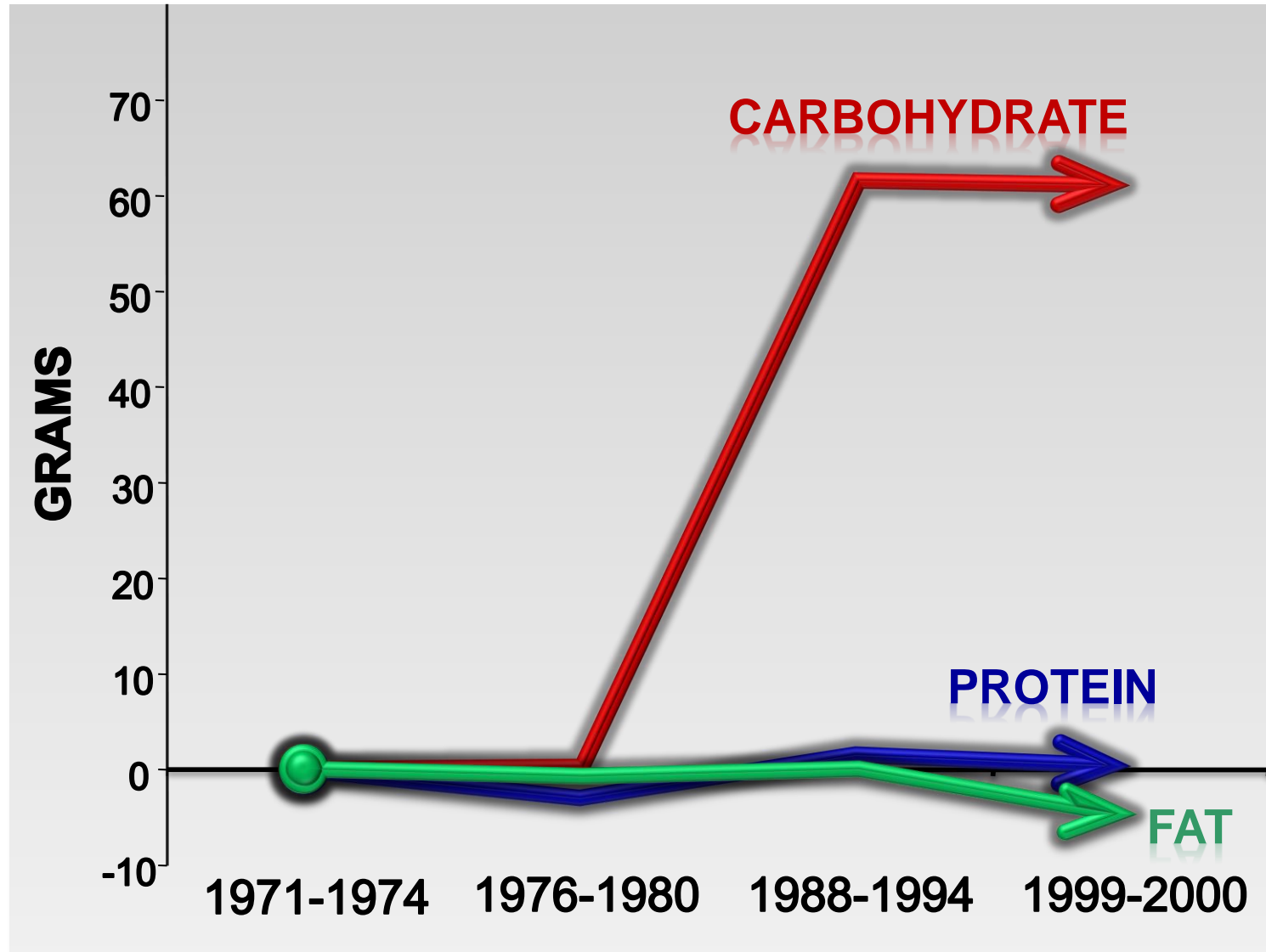
# Type-2 Diabetes from a carbohydrate perspective

- ❑ A disease of insulin resistance defined by some combination of hyperglycemia & hyperinsulinemia
- ❑ Characteristics:
  - Insulin Resistance = Carb Intolerance
  - Inherited condition triggered by over-consumption of carbs
  - Inflammatory antecedents
  - Correlated with but not caused by obesity
- ❑ Current treatment paradigm
  - Give 60 g carbs/meal
  - Use medications to maintain euglycemia





# The majority of Americans consume too many sugars/starches relative to their tolerance





# Eating too many carbs manifests in an insulin resistant phenotype



## THE METABOLIC SYNDROME



HEART DISEASE



LIPID PROBLEMS



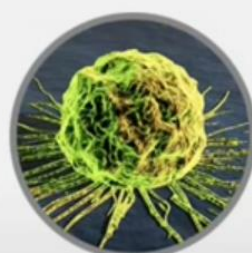
HYPERTENSION



TYPE 2 DIABETES



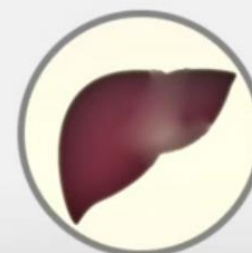
DEMENTIA



CANCER



POLYCYSTIC  
OVARIAN  
SYNDROME



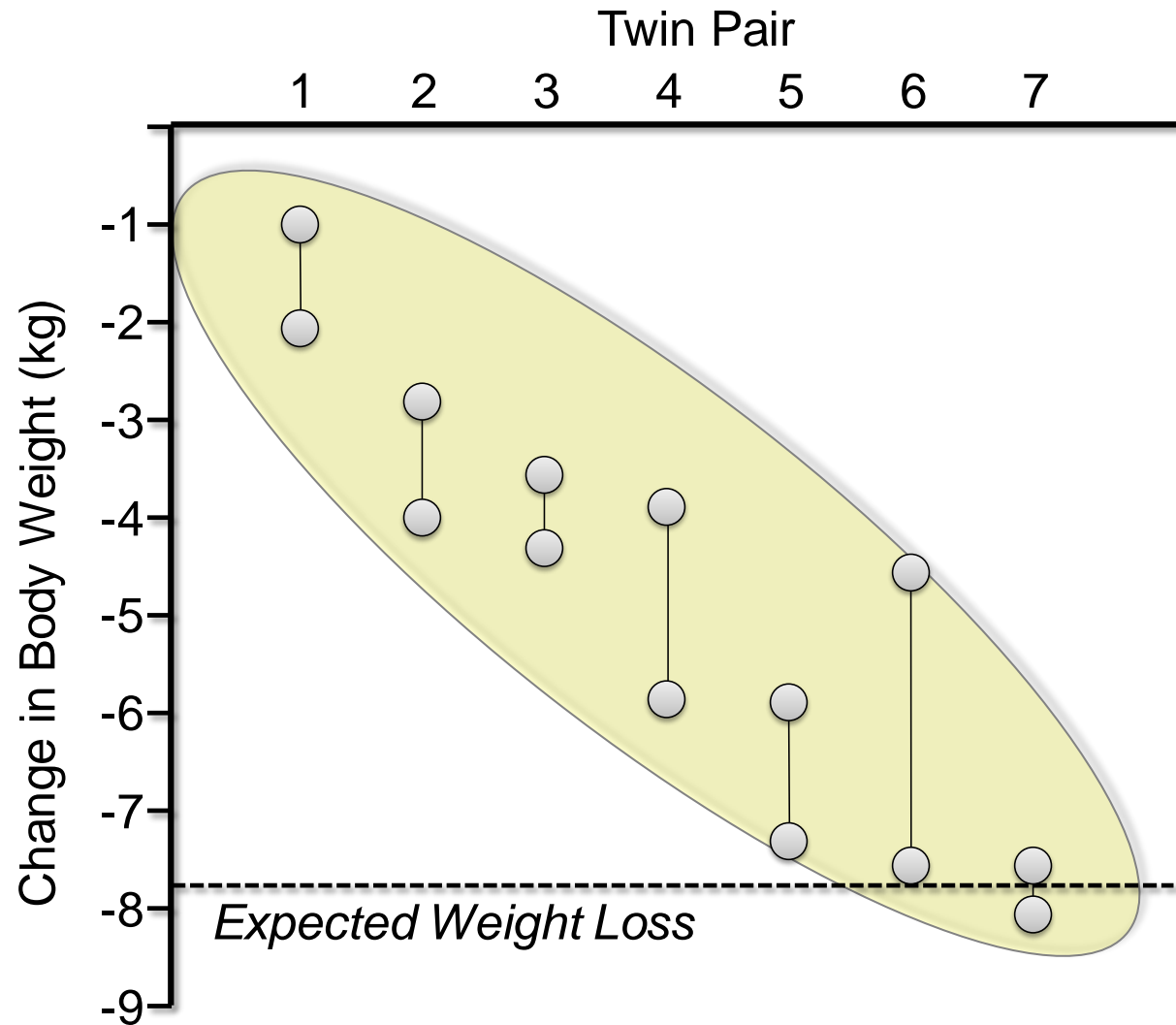
NON-ALCOHOLIC  
FATTY LIVER  
DISEASE

# Principle of Human Carbohydrate Intolerance

- Stems from >2 million years of evolution when most humans had limited exposure to sugars/starches
- Now that carb-based foods are ubiquitous, most of us show signs of metabolic dysfunction
- For a few, a modest ↓ carbs suffices to prevent overt illness
- But in many, metabolic correction requires greater carb restriction that results in **KETO-ADAPTATION**

# Exercise is a poor weight loss tool for some

- Identical twins exercised twice a day (9 days out of 10) for 93 days (daily deficit of 624 kcal/d)



FOR TODAY

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Obesity & diabetes epidemics

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**Ketones and keto-adaptation defined**

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Keto-adaptation reverses prediabetes & diabetes

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Beyond obesity & diabetes

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# Principles of a Well-Formulated Ketogenic Diet

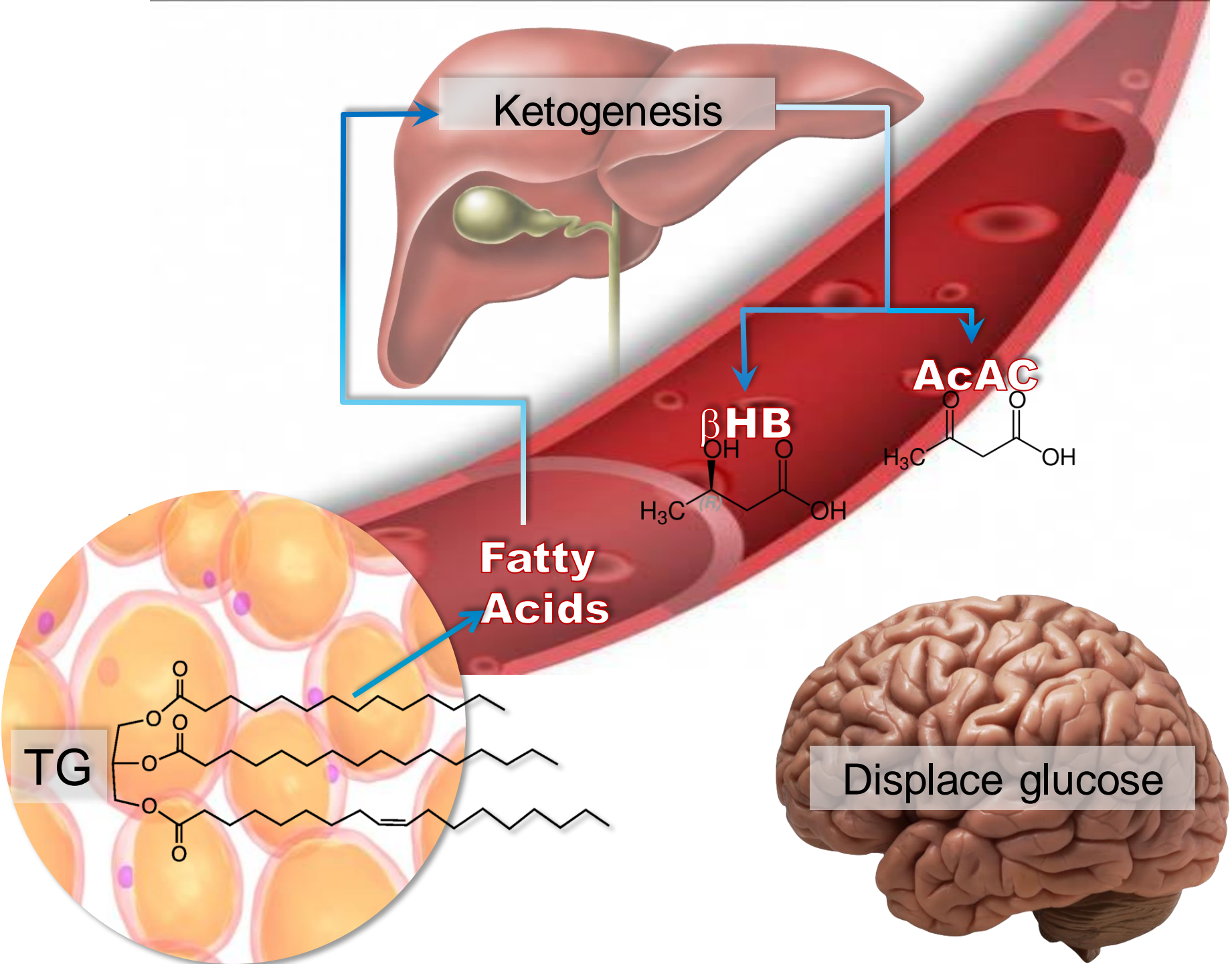
***Most either contradict current conventional wisdom or are unknown to mainstream healthcare***

- Carb restriction to  $\uparrow$  ketones  $>0.5$  mmol/L
- Moderate, not high, protein (15-20% of energy expenditure)
- Sodium, potassium, magnesium, zinc nutriture are critical to well-being and function
- A weight maintenance ketogenic diet is necessarily high fat
- Not all dietary fat are equal (MUFA & SFA are preferred cellular fuels; PUFA are essential but like fat soluble vitamins are poorly tolerated at high intakes)
- Saturated fats should be embraced rather than avoided
- Dietary cholesterol is not a health risk
- Satiety is a robust indicator of appropriate dietary energy intake



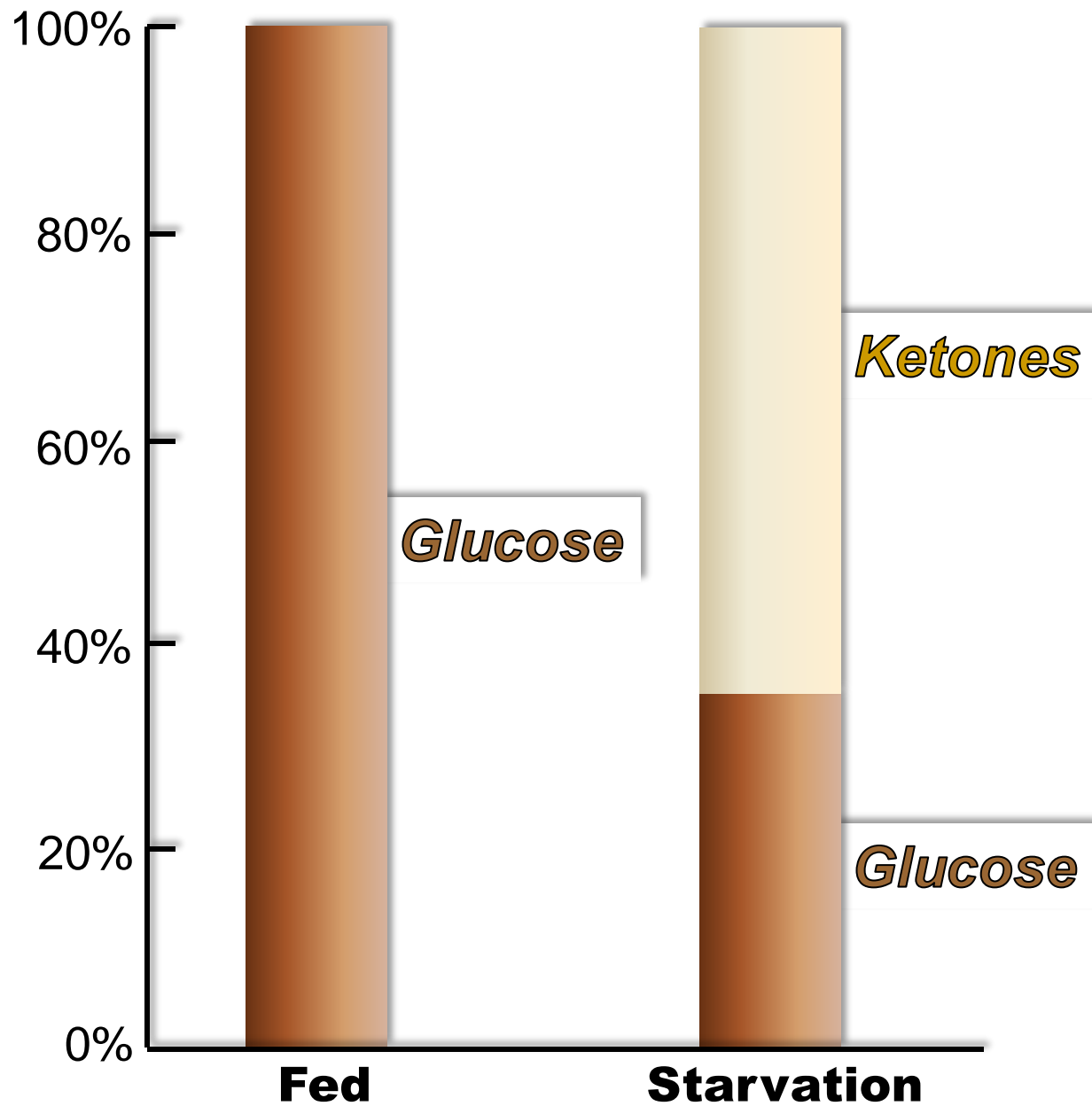








# Brain readily adapts to using ketones



# The New Science of Ketones

## Suppression of Oxidative Stress by $\beta$ -Hydroxybutyrate, an Endogenous Histone Deacetylase Inhibitor

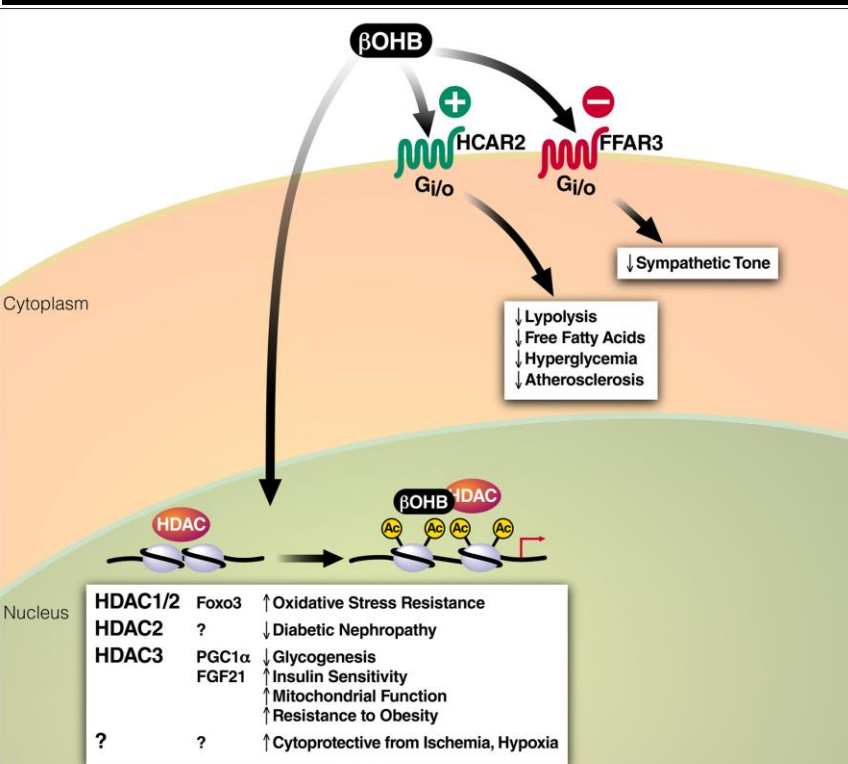
Tadahiro Shimazu<sup>1,2</sup>, Matthew D. Hirschey<sup>1,2</sup>, John Newman<sup>1,2</sup>, Wenjuan He<sup>1,2</sup>, Kotaro Shirakawa<sup>1,2</sup>, Natacha

+ See all authors and affiliations

Science 11 Jan 2013;  
Vol. 339, Issue 6116, pp. 211-214  
DOI: 10.1126/science.1227166

Reduced  
oxidative stress  
& inflammation

Possible direct  
effects on insulin  
resistance



Diabetes Research and Clinical Practice

Volume 106, Issue 2, November 2014, Pages 173-181

Invited Review

$\beta$ -hydroxybutyrate: Much more than a metabolite

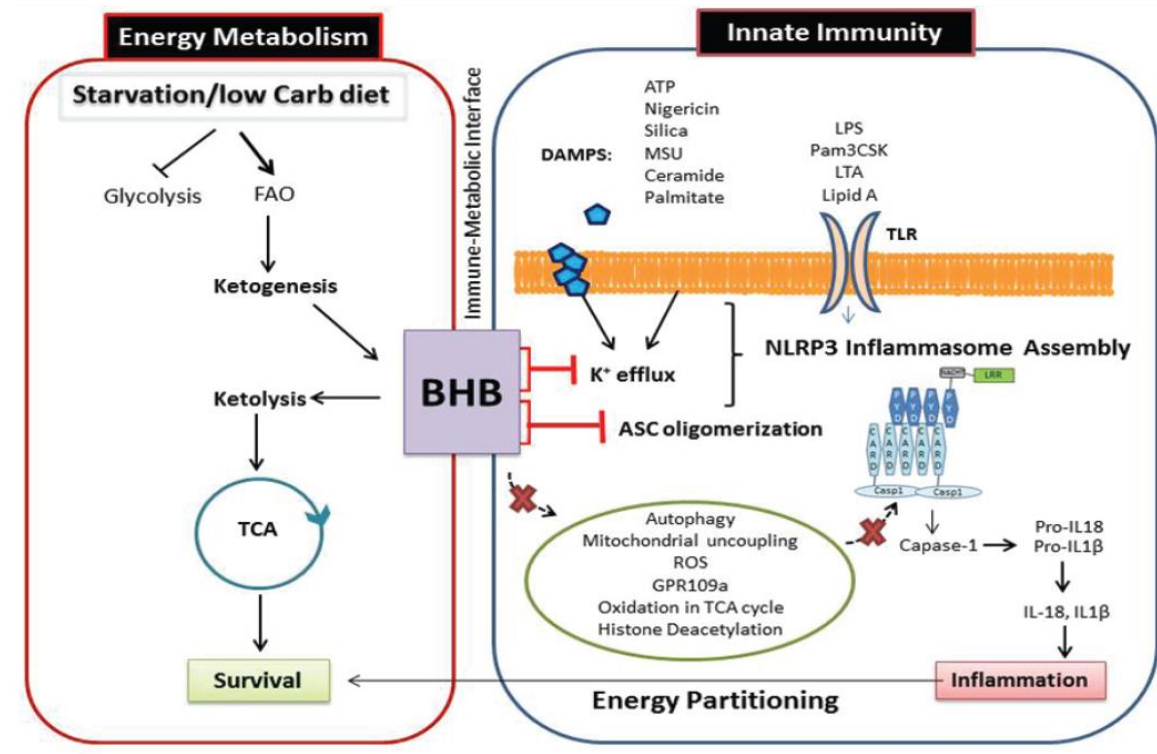
John C. Newman<sup>a, b</sup>, Eric Verdin<sup>b</sup> ✉

# Ketones decrease inflammation/oxidative stress

**nature  
medicine**

## The ketone metabolite $\beta$ -hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease

Yun-Hee Youm<sup>1,11</sup>, Kim Y Nguyen<sup>1,11</sup>, Ryan W Grant<sup>2</sup>, Emily L Goldberg<sup>1</sup>, Monica Bodogai<sup>3</sup>, Dongin Kim<sup>4</sup>, Dominic D'Agostino<sup>5</sup>, Noah Planavsky<sup>6</sup>, Christopher Lupfer<sup>7</sup>, Thirumala D Kanneganti<sup>7</sup>, Seokwon Kang<sup>8</sup>, Tamas L Horvath<sup>1</sup>, Tarek M Fahmy<sup>4</sup>, Peter A Crawford<sup>9</sup>, Arya Biragyn<sup>3</sup>, Emad Alnemri<sup>8</sup> & Vishwa Deep Dixit<sup>1,10</sup>



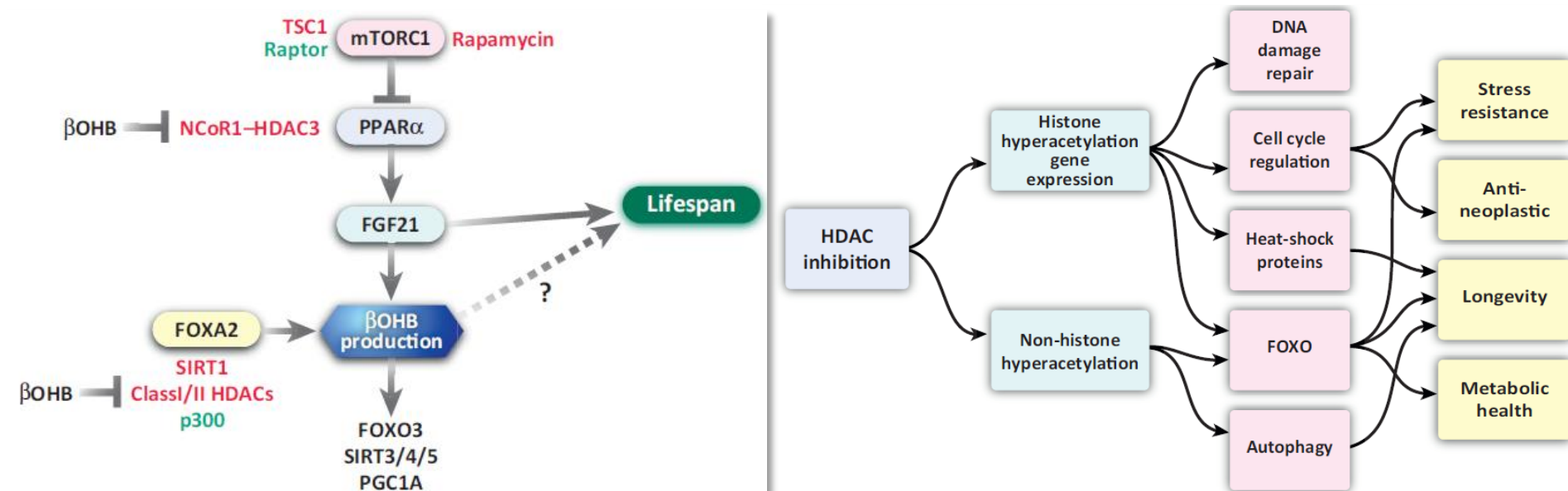
# Increased Longevity – A Credible Benefit Of Nutritional Ketosis?

## Critical Review

### Ketone Bodies Mimic the Life Span Extending Properties of Caloric Restriction



Richard L. Veech<sup>1\*</sup>  
Patrick C. Bradshaw<sup>2</sup>  
Kieran Clarke<sup>3</sup>  
William Curtis<sup>1</sup>  
Robert Pawlosky<sup>1</sup>  
M. Todd King<sup>1</sup>

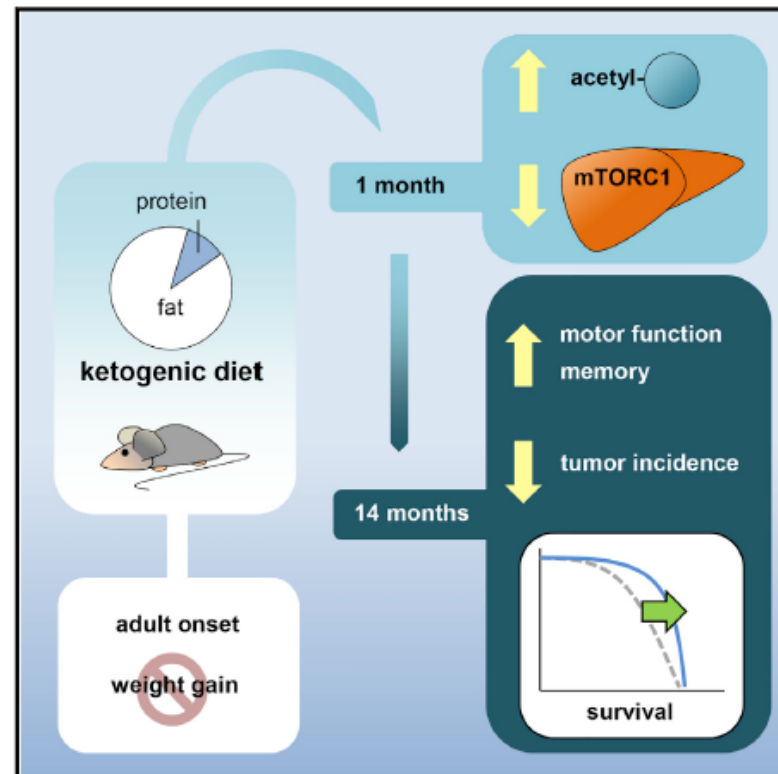


# Increased Longevity – A Credible Benefit Of Nutritional Ketosis?

## Cell Metabolism

### A Ketogenic Diet Extends Longevity and Healthspan in Adult Mice

#### Graphical Abstract



#### Authors

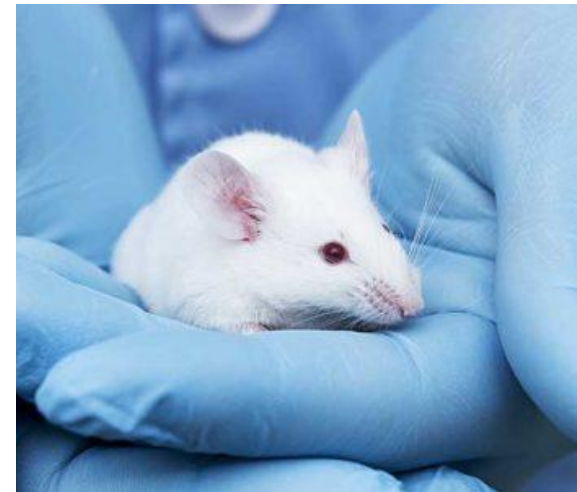
Megan N. Roberts, Marita A. Wallace, Alexey A. Tomilov, ..., Gino A. Cortopassi, Jon J. Ramsey, Jose Alberto Lopez-Dominguez

#### Correspondence

[jjramsey@ucdavis.edu](mailto:jjramsey@ucdavis.edu) (J.J.R.),  
[jlopez-dominguez@buckinstitute.org](mailto:jlopez-dominguez@buckinstitute.org) (J.A.L.-D.)

#### In Brief

Roberts et al. show that a ketogenic diet extends longevity in adult male mice and preserves motor function, memory, and muscle mass in aged mice. The ketogenic diet increased protein acetylation levels and regulated mTORC1 signaling in a tissue-dependent manner. See related paper by Newman et al.

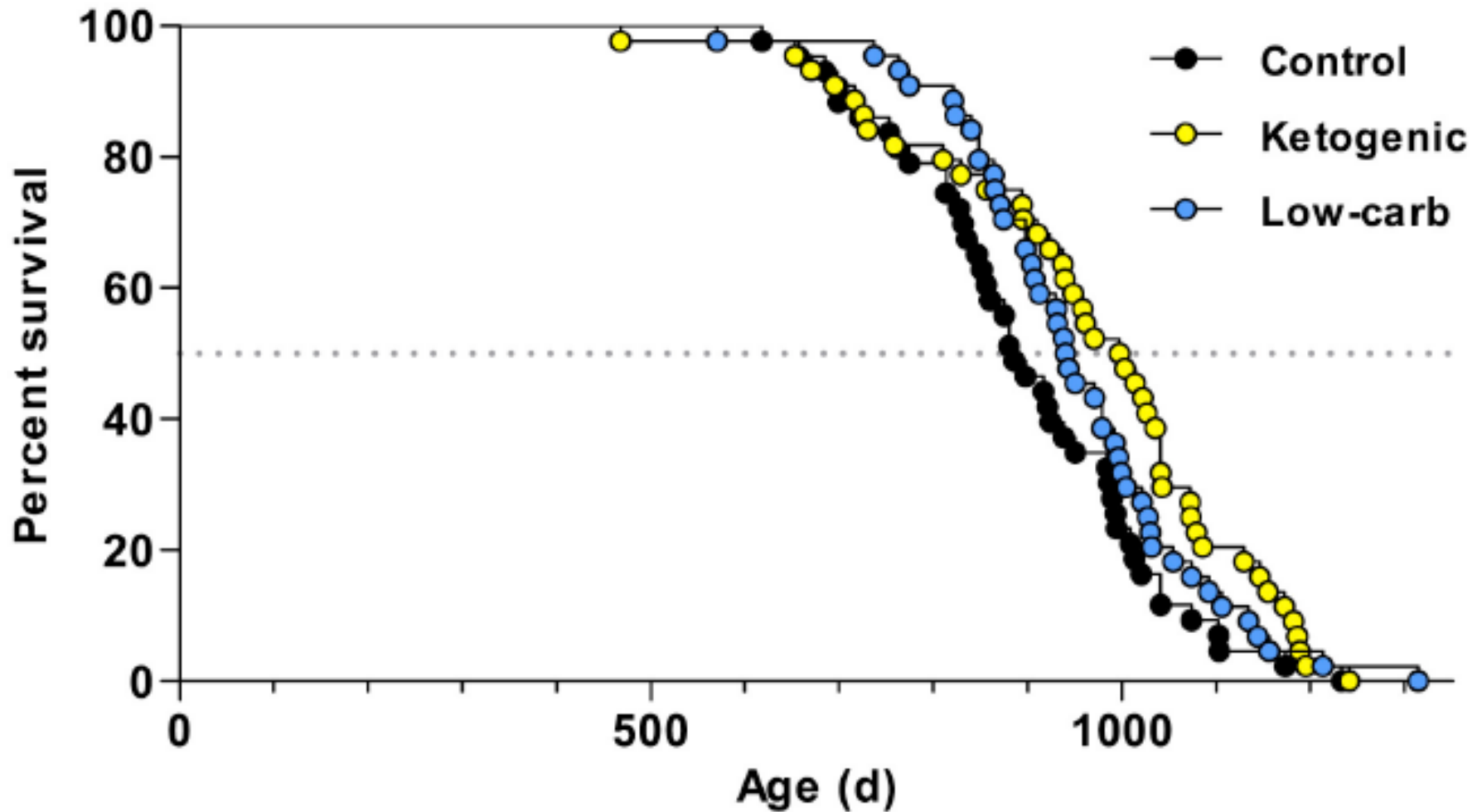


## Median life spans (days)

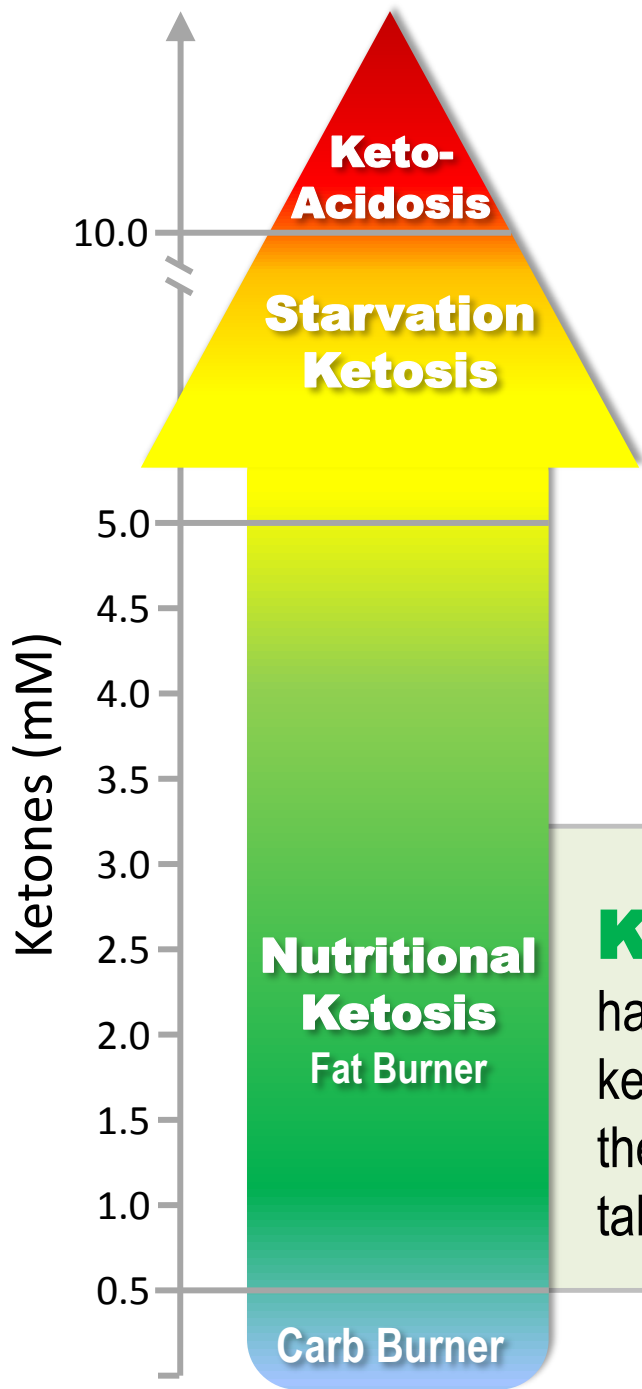
Control = 886

Low-Carb = 943

Ketogenic = 1003

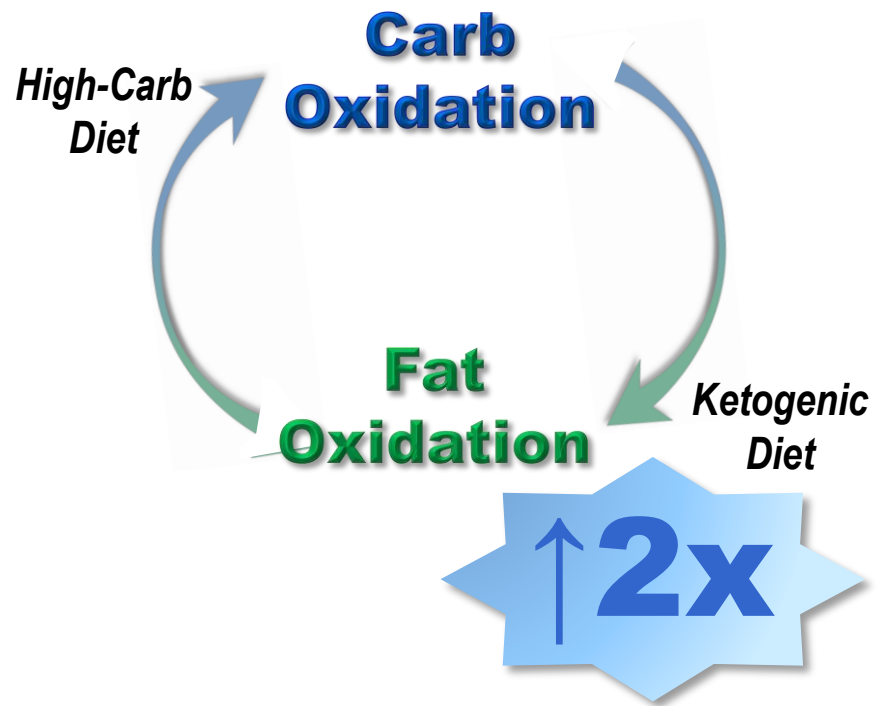
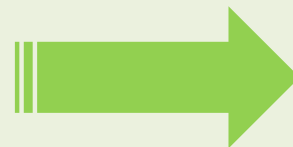






## Keto-Adaptation

happens when you are in nutritional ketosis over consecutive weeks; the full spectrum of adaptations may take months/years.





# **Keto-Adaptation**

**...ancient metabolic blue print hard-wired into our genetic code over a couple million years of human evolution.**

**...associated with broad spectrum health benefits.**

FOR TODAY

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Obesity & diabetes epidemics

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Ketones and keto-adaptation defined

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**Keto-adaptation reverses prediabetes & diabetes**

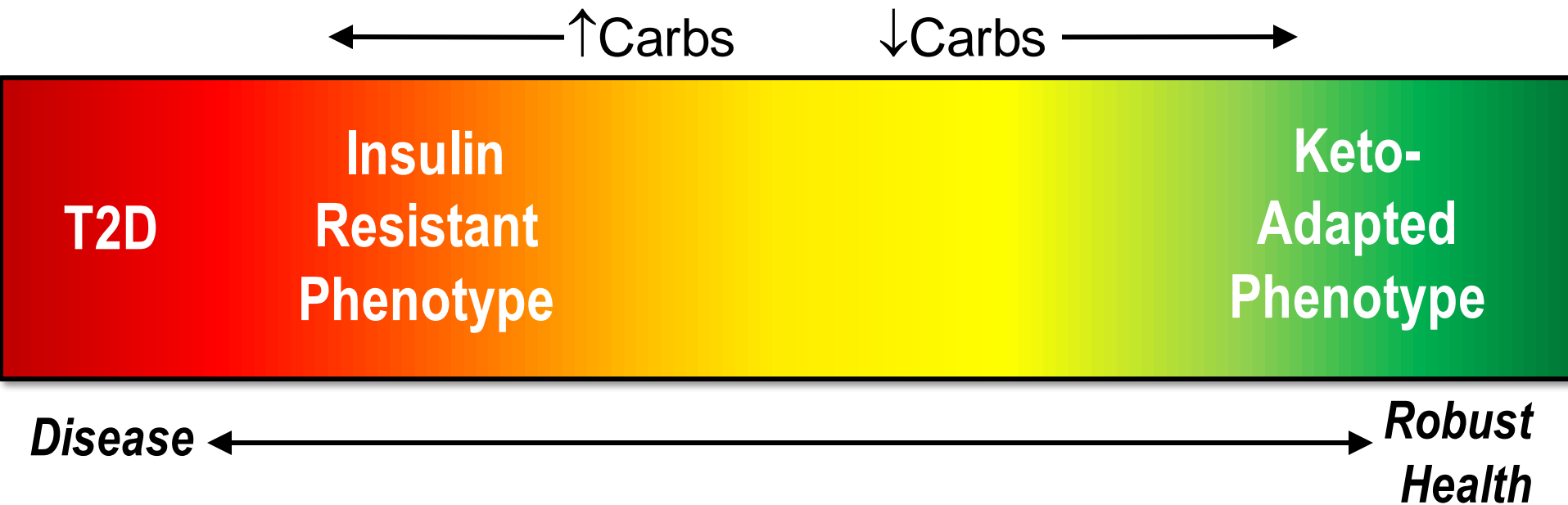
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Beyond obesity & diabetes

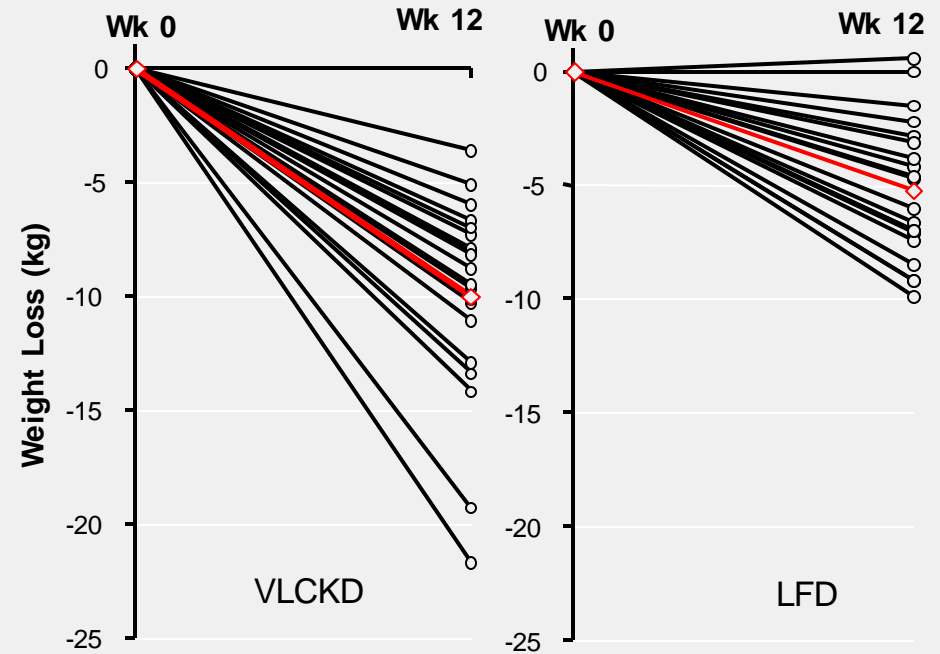
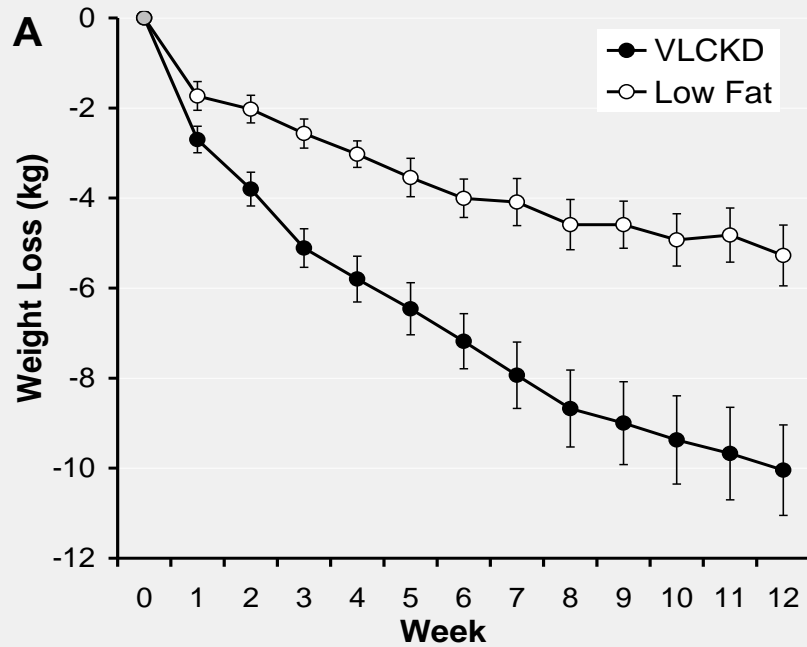
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# Insulin Resistance & Keto-Adaptation: Opposite Ends of a Phenotypic Continuum



# A ketogenic diet enhances weight loss



# Meta-analyses consistently show benefits of ketogenic diets on weight loss



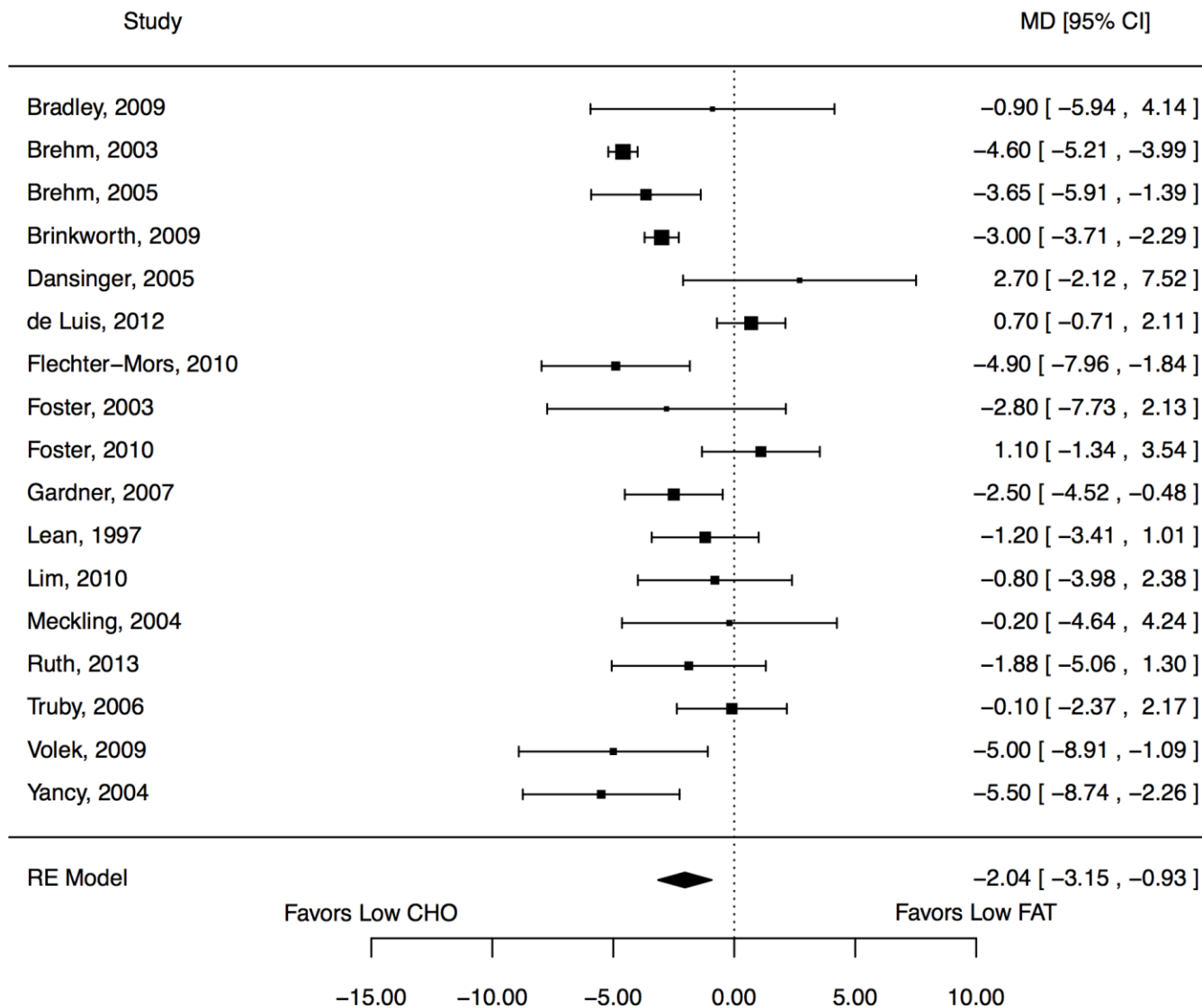
## Dietary Intervention for Overweight and Obese Adults: Comparison of Low-Carbohydrate and Low-Fat Diets. A Meta-Analysis

Jonathan Sackner-Bernstein<sup>1\*</sup>, David Kanter<sup>2</sup>, Sanjay Kaul<sup>3</sup>

### Conclusions

This trial-level meta-analysis of randomized controlled trials comparing LoCHO diets with LoFAT diets in strictly adherent populations demonstrates that each diet was associated with significant weight loss and reduction in predicted risk of ASCVD events. However, LoCHO diet was associated with modest but significantly greater improvements in weight loss and predicted ASCVD risk in studies from 8 weeks to 24 months in duration. These results suggest that future evaluations of dietary guidelines should consider low carbohydrate diets as effective and safe intervention for weight management in the overweight and obese, although long-term effects require further investigation.

## Difference in Weight Loss (RCTs)

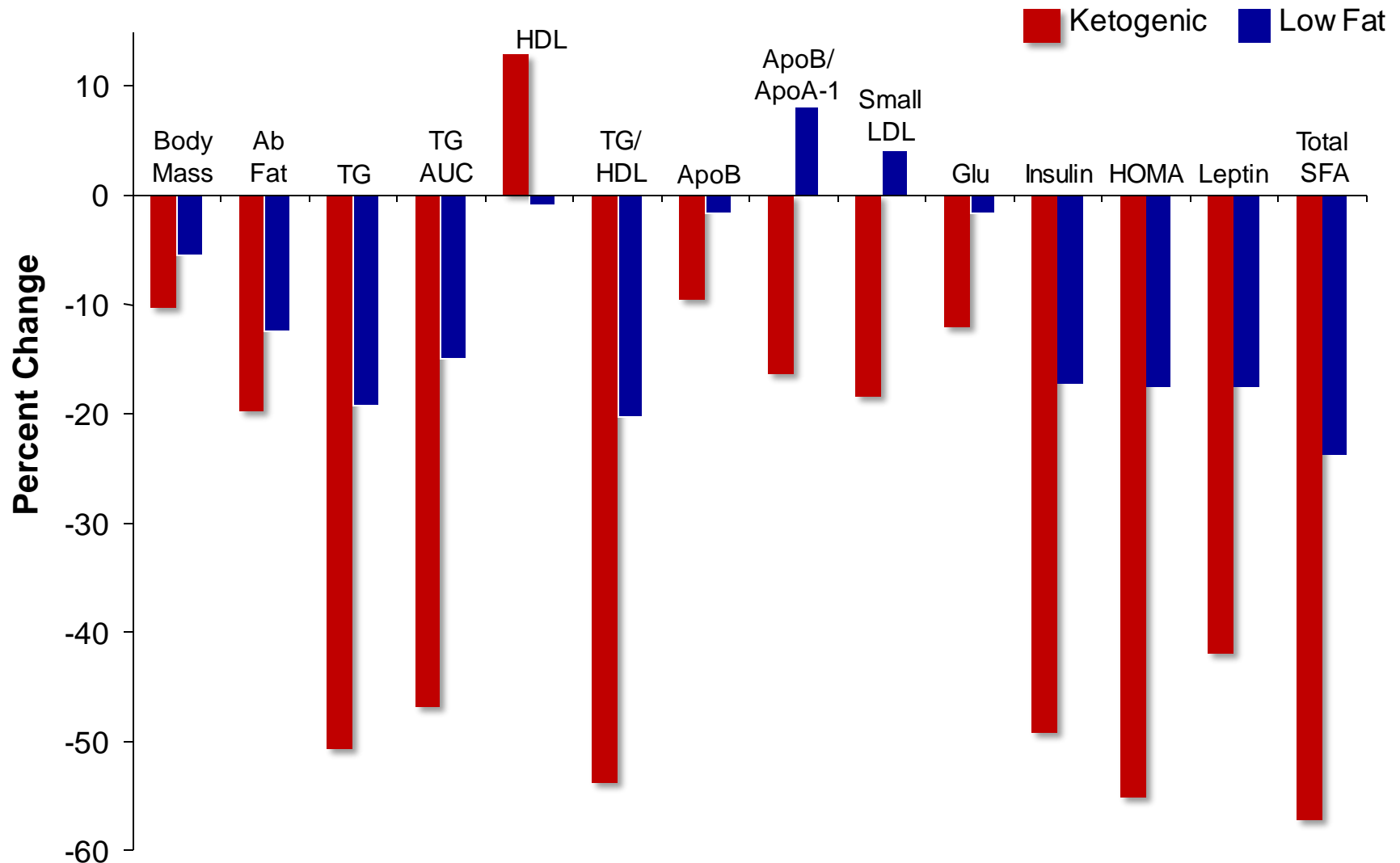


# Weight Loss





# Keto-Adaptation Reverses Metabolic Syndrome

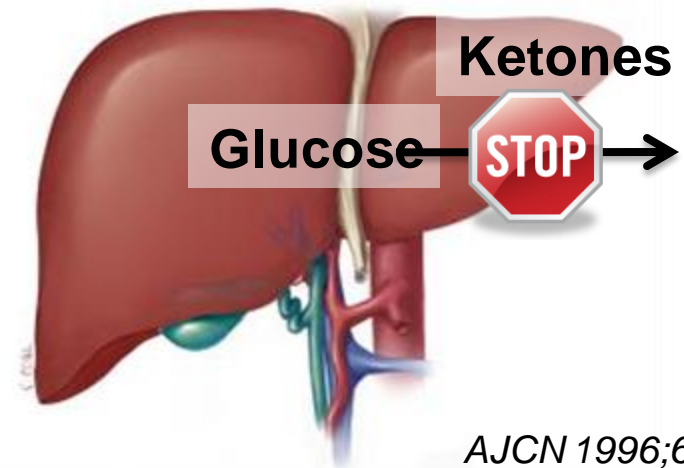
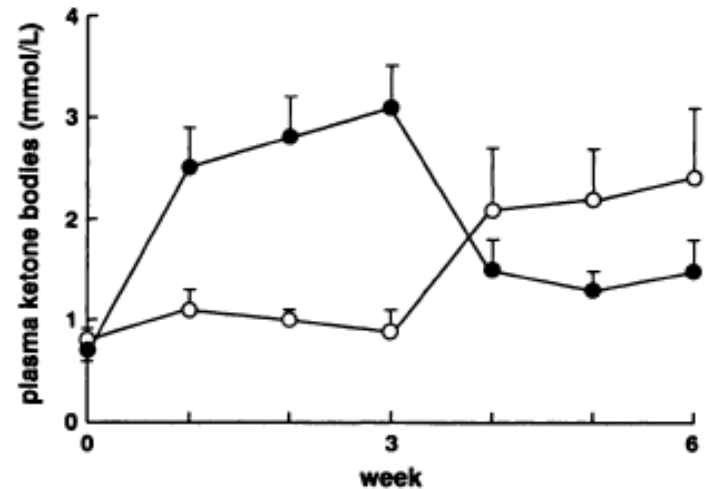


*Results after 3 months in 40 subjects with metabolic syndrome randomized to either a ketogenic or low fat diet (Forsythe et al. 2008).*

# Effects of diet composition and ketosis on glycemia during very-low-energy-diet therapy in obese patients with non-insulin-dependent diabetes mellitus<sup>1-3</sup>

Barry Gumbiner, Jacqueline A Wendel, and Michael P McDermott

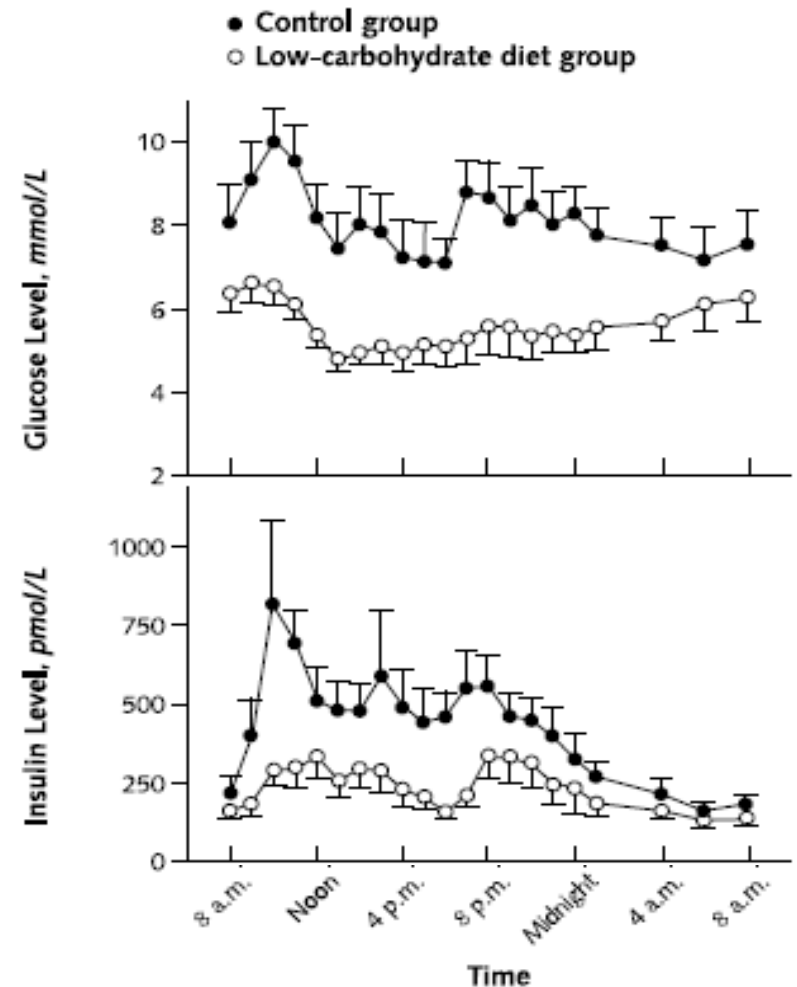
- Obese T2D fed 2 diets for 3 wk
- Diets matched for energy (650 kcal) and protein but carbohydrate was low (24 g) or high (94 g)
- Fasting and OGTT glycemia lower after **Ketogenic** diet
- Hepatic glucose output (HGO) 22% lower after **Ketogenic** diet
- Strong correlation between plasma ketones and HGO



# Effect of a Low-Carbohydrate Diet on Appetite, Blood Glucose Levels, and Insulin Resistance in Obese Patients with Type 2 Diabetes

Guenther Boden, MD; Karin Sargrad, MS, RD, CDE; Carol Homko, PhD, RN, CDE; Maria Mozzoli, BS; and T. Peter Stein, PhD

- Inpatient study in obese T2D
- Fed **ketogenic**(<20 g CHO/d) diet for 2 wk
- Plasma glucose 7.5 to 6.3 mmol/L
- Hemoglobin A<sub>1c</sub> 7.3 to 6.8%
- Highly significant improvements (75%) in insulin sensitivity (euglycemic hyperinsulinemic clamp)





ELSEVIER

Contents lists available at ScienceDirect

# Nutrition

journal homepage: [www.nutritionjournal.com](http://www.nutritionjournal.com)



## Critical Review

# Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base



Richard D. Feinman Ph.D.<sup>a,\*</sup>, Wendy K. Pogozielski Ph.D.<sup>b</sup>, Arne Astrup M.D.<sup>c</sup>,  
Richard K. Bernstein M.D.<sup>d</sup>, Eugene J. Fine M.S., M.D.<sup>e</sup>,  
Eric C. Westman M.D., M.H.S.<sup>f</sup>, Anthony Accurso M.D.<sup>g</sup>, Lynda Frassetto M.D.<sup>h</sup>,  
Barbara A. Gower Ph.D.<sup>i</sup>, Samy I. McFarlane M.D.<sup>j</sup>, Jørgen Vesti Nielsen M.D.<sup>k</sup>,  
Thure Krarup M.D.<sup>l</sup>, Laura Saslow Ph.D.<sup>m</sup>, Karl S. Roth M.D.<sup>n</sup>, Mary C. Vernon M.D.<sup>o</sup>,  
Jeff S. Volek R.D., Ph.D.<sup>p</sup>, Gilbert B. Wilshire M.D.<sup>q</sup>, Annika Dahlqvist M.D.<sup>r</sup>,  
Ralf Sundberg M.D., Ph.D.<sup>s</sup>, Ann Childers M.D.<sup>t</sup>, Katharine Morrison M.R.C.G.P.<sup>u</sup>,  
Anssi H. Manninen M.H.S.<sup>v</sup>, Hussain M. Dashti M.D., Ph.D., F.A.C.S., F.I.C.S.<sup>w</sup>,  
Richard J. Wood Ph.D.<sup>x</sup>, Jay Wortman M.D.<sup>y</sup>, Nicolai Worm Ph.D.<sup>z</sup>

# Keto-Adaptation Reverses Type-2 Diabetes

JMIR DIABETES

McKenzie et al

Original Paper

## A Novel Intervention Including Individualized Nutritional Recommendations Reduces Hemoglobin A1c Level, Medication Use, and Weight in Type 2 Diabetes

Amy L McKenzie<sup>1</sup>, PhD; Sarah J Hallberg<sup>1,2</sup>, DO, MS; Brent C Creighton<sup>1</sup>, PhD; Brittanie M Volk<sup>1</sup>, RD, PhD; Theresa M Link<sup>1</sup>, RD, CDE; Marcy K Abner<sup>1</sup>, RD; Roberta M Glon<sup>1</sup>, RN, BSN; James P McCarter<sup>1</sup>, MD, PhD; Jeff S Volek<sup>1</sup>, RD, PhD; Stephen D Phinney<sup>1</sup>, MD, PhD

***JMIR Diabetes. 2017;2(1):e5, published March 7, 2017.***



CLINICAL TRIAL

# Patients

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**N = 378**

262 with type 2 diabetes  
(T2D)

116 with pre-diabetes

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## Location

Greater Lafayette, Indiana

## T2D Mean Characteristics

Starting age: 54 yrs

Starting BMI: 41 kg/m<sup>2</sup>

Starting weight: 257 lbs  
(117 kg)

67% female

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# Key Results

For the N=262 T2DM participants at 10 wk. Intent to treat analysis & completers analysis.

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**1.0** Average reduction in HbA1c (from 7.6 to 6.6)

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**87%** Eliminated or reduced insulin

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**56%** Reduced HbA1c < 6.5\*

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**75%** Of completers experienced clinically significant weight loss of >5%

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**91%** Completed Virta protocol

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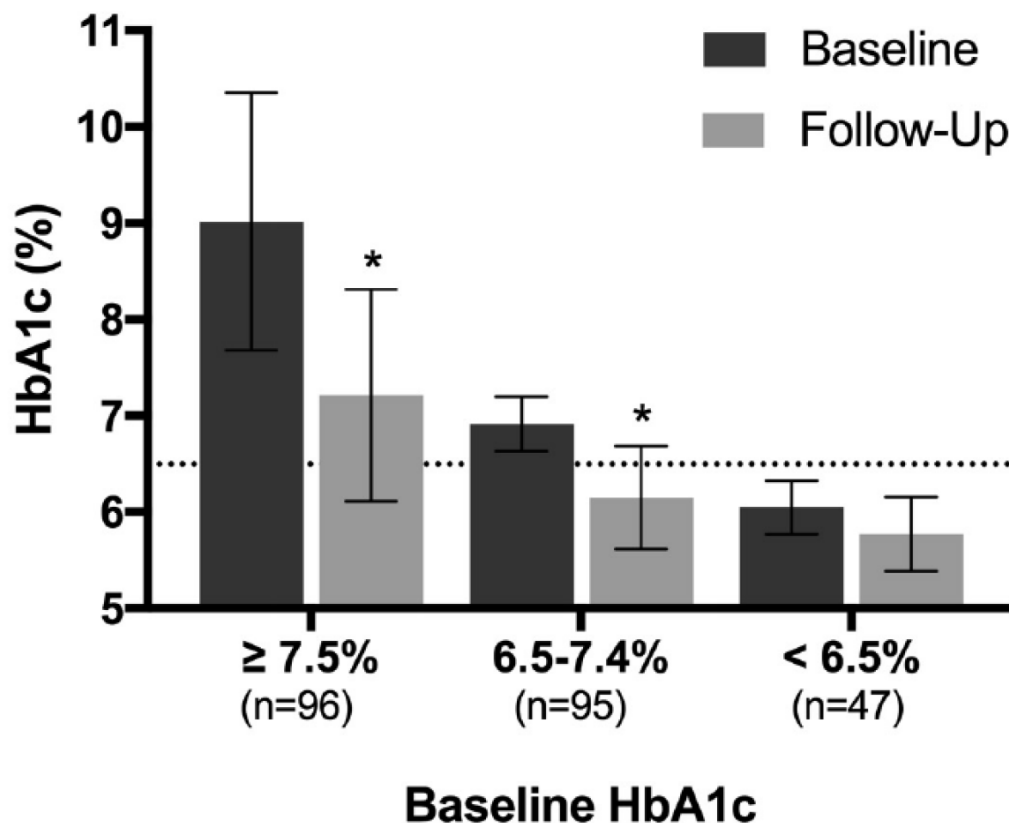
**20%** Average reduction in triglycerides

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*\* 48% Reduced A1c < 6.5 and eliminated all diabetes medications or used metformin only*

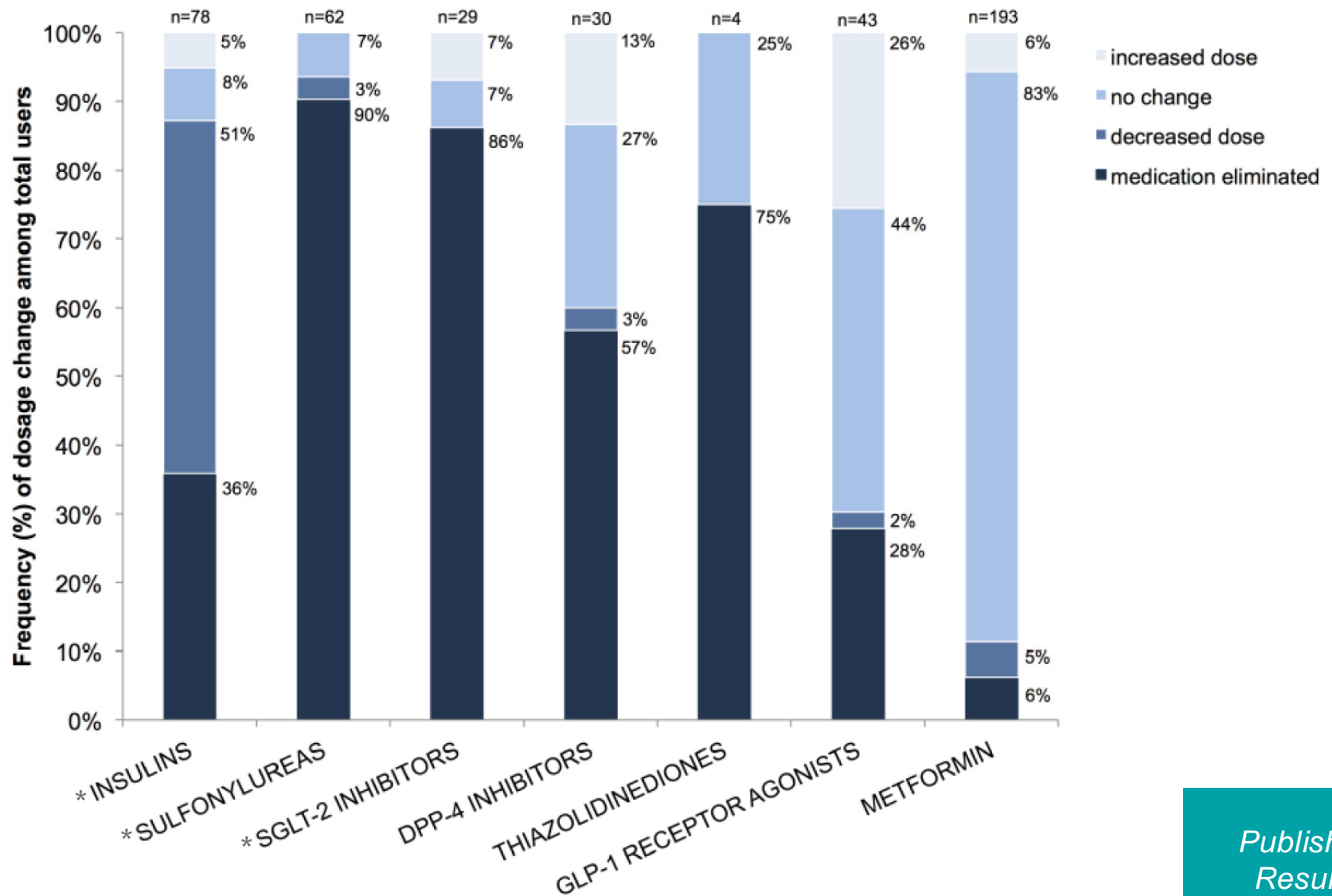


## Trial at 70 days : HbA1c is Substantially Reduced

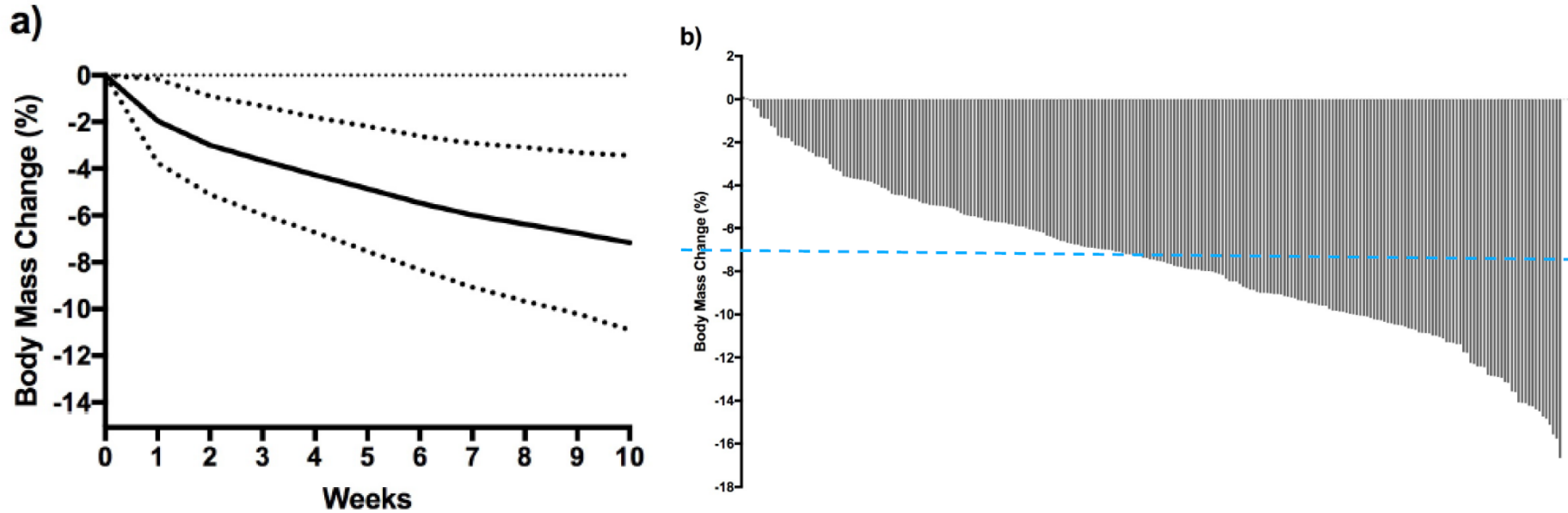


- Completers improved HbA1c by  $1.1 \pm 1.1\%$  in the first 10–11 weeks, from  $7.6 \pm 1.5\%$  at baseline to  $6.5 \pm 1.0\%$  ( $P < 0.001$ )
- This is a dramatic reduction in HbA1c, while withdrawing medications

# Trial at 70 days : Medications Are Substantially Reduced & Eliminated



## Trial at 70 days : Weight Loss is Significant at 10 weeks. Rate of loss is modest at ~2 lbs a week.



- Mean weight loss of 7.2% (~19 lbs by 10 weeks)
- 75% of completers experienced clinically significant weight loss of >5%
- Only 5 of 262 subjects registered a weight gain (2 completers, 3 non-completers)

# 1-year Outcomes

FOR TODAY

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Obesity & diabetes epidemics

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Keto-adaptation reverses prediabetes & diabetes

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**Beyond obesity & diabetes**

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# Promising Research Exploring the Therapeutic Use of Ketogenic Diets

## Adult Obesity

**Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials**

## Fatty Liver

**The Effect of a Low-Carbohydrate, Ketogenic Diet on Nonalcoholic Fatty Liver Disease: A Pilot Study**

David Tendler · Sauyu Lin · William S. Yancy Jr. ·

## Pediatric Obesity

**Efficacy and Safety of a High Protein, Low Carbohydrate Diet for Weight Loss in Severely Obese Adolescents**

Nancy F. Krebs, MD, MS, Dexiang Gao, PhD, Jane Gralla, PhD, Juliet S. Collins, MD, and Susan L. Johnson, PhD

## Cancer

**Targeting insulin inhibition as a metabolic therapy in advanced cancer: A pilot safety and feasibility dietary trial in 10 patients**

Eugene J. Fine M.D., M.S.<sup>a,\*</sup>, C.J. Segal-Isaacson Ed.D., R.D.<sup>b</sup>, Richard D. Feinman Ph.D.<sup>c</sup>,

## Type-2 Diabetes

**Reversal of Diabetic Nephropathy by a Ketogenic Diet**

Michal M. Poplawski<sup>1</sup>, Jason W. Mastaitis<sup>2</sup>, Fumiko Isoda<sup>1</sup>, Fabrizio Grosjean<sup>3</sup>, Feng Zheng<sup>3</sup>, Charles V.

## Type-1 Diabetes

**Low carbohydrate diet in type 1 diabetes, long-term improvement and adherence: A clinical audit**

Jørgen Vest Nielsen<sup>1\*</sup>, Caroline Gando<sup>2</sup>, Eva Joensson<sup>2</sup> and Carina Paulsson<sup>2</sup>

## Autism

**Potential therapeutic use of the ketogenic diet in autism spectrum disorders**

Eleonora Napoli<sup>1\*</sup>, Nadia Dueñas<sup>1</sup> and Cecilia Giulivi<sup>1,2</sup>

## Polycystic Ovary Syndrome (PCOS)

**The effects of a low-carbohydrate, ketogenic diet on the polycystic ovary syndrome: A pilot study**

John C Mavropoulos<sup>1</sup>, William S Yancy<sup>1,2</sup>, Juanita Hepburn<sup>1</sup> and

## Alzheimer's Disease

**A ketone ester diet exhibits anxiolytic and cognition-sparing properties, and lessens amyloid and tau pathologies in a mouse model of Alzheimer's disease**

Yoshihiro Kashiwaya<sup>a</sup>, Christian Bergman<sup>a</sup>, Jong-Hwan Lee<sup>b</sup>, Ruiqian Wan<sup>c</sup>, M. Todd King<sup>a</sup>,

## Epilepsy

**Therapeutic Success of the Ketogenic Diet as a Treatment Option for Epilepsy: a**

**Meta-analysis**

Hai-feng Li<sup>1</sup>, MM; Yan Zou<sup>2</sup>, MPH; Gangqiang Ding<sup>2</sup>, MD

## Hypertension/Vascular Function

**Dietary carbohydrate restriction improves insulin sensitivity, blood pressure, microvascular function, and cellular adhesion markers in individuals taking statins<sup>☆</sup>**

Kevin D. Ballard<sup>a</sup>, Erin E. Quann<sup>a</sup>, Brian R. Kupchak<sup>a</sup>, Brittanie M. Volk<sup>a</sup>,

## Parkinson Disease

**Treatment of Parkinson disease with diet-induced hyperketonemia: A feasibility study**

T. B. VanItallie, C. Nonas, A. Di Rocco, K. Boyar, K. Hyams and S. B. Heymsfield



# Debunking long-standing dogma in sports nutrition



**Chris Froome**  
*Tour de France Champion*



**Tim Olsen Wins**  
2012 Western States 100



**Zach Bitter**  
American 100 Mile Track  
Record Holder (11:40:55)



**Mike Morton**  
American 24-hr Distance  
Running Record (172 Miles)

# Faster Study

## *Fat Adapted Substrate Oxidation in Trained Elite Runners*

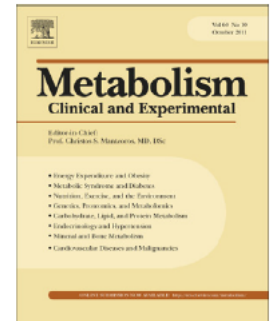
METABOLISM CLINICAL AND EXPERIMENTAL 65 (2016) 100–110



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

# Metabolism

[www.metabolismjournal.com](http://www.metabolismjournal.com)



## Metabolic characteristics of keto-adapted ultra-endurance runners



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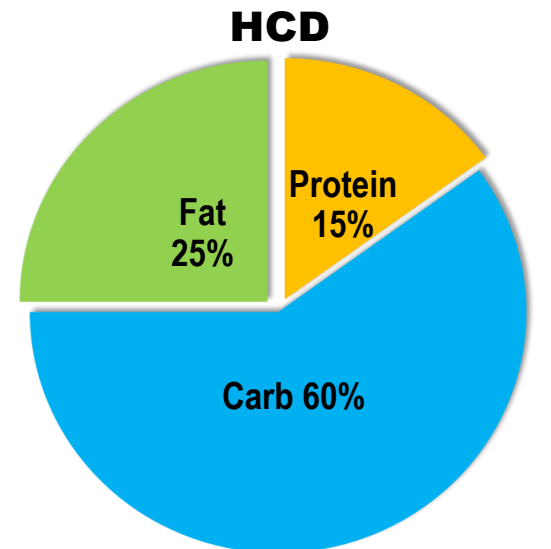
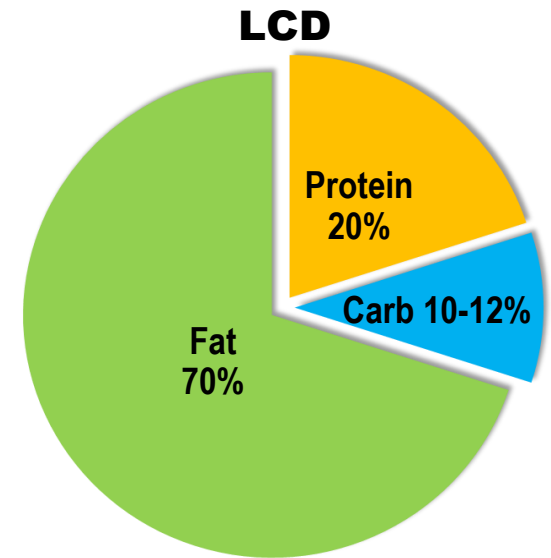


# Aim

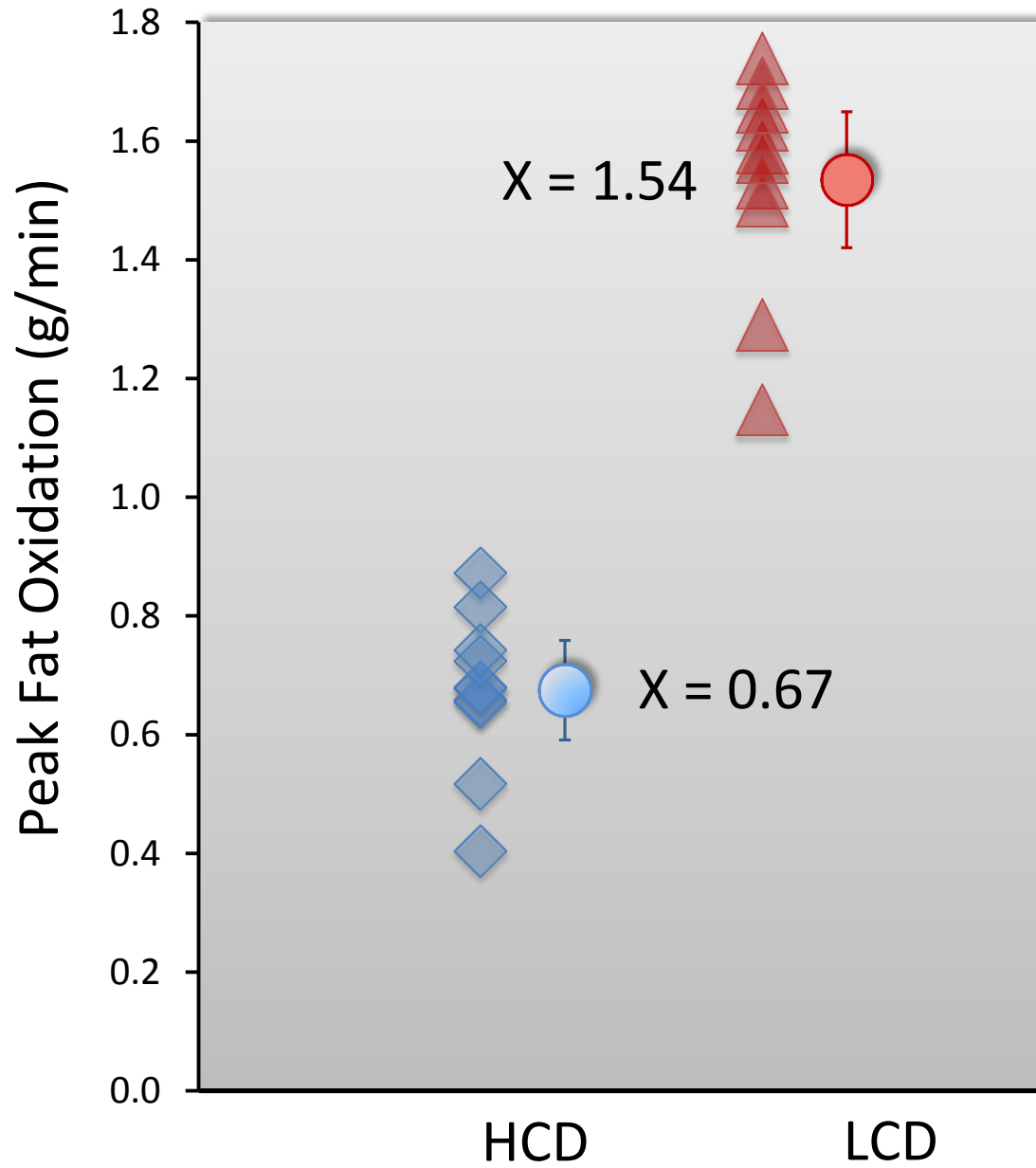
*Take a deeper look into the keto-adapted athlete*



	<b>HCD (n = 10)</b>		<b>LCD (n = 10)</b>	
	Mean	Range	Mean	Range
Age (yr)	33	22 - 40	34	21 - 45
Height (cm)	173.9	167.1 – 182.0	175.7	165.1 – 189.4
Body mass (kg)	66.5	57.9 - 79.9	68.8	55.5 - 81.6
Body fat (%)	9.6	4.7 - 15.5	7.8	4.5 - 12.3
Fat mass (g)	6,513	2,774 – 12,102	5,454	2,953 – 8,780
Lean mass (kg)	57.3	49.4 -64.2	60.9	50.2 – 71.7
VO <sub>2</sub> max (mL/kg/min)	64.3	54.8 – 76.0	64.7	59.6 – 71.1
VO <sub>2</sub> max (L/min)	4.25	3.34 – 4.86	4.41	3.78 – 4.95



# Peak Fat Burning



## SUMMARY

1. **Ketosis & keto-adaption are natural, if not preferred, metabolic states for humans**
2. **Because it gets at the root problem, sustained nutritional ketosis has broad applications for managing diseases that manifest from insulin resistance**
3. **T2D and prediabetes are reversible**

## **OSU Conference on Carbohydrate Restriction & Nutritional Ketosis** *(Aug 16-17, 2018)*

- International experts from a variety of disciplines:
  - Aging/Longevity
  - Cancer
  - Type 1 and 2 diabetes
  - Neurology
  - Performance
  - Ketones as signals
  - Inflammation/oxidative stress
  - Exogenous ketones
  - Obesity/dyslipidemia
  - Epidemiology