

INTRODUCTION TO NUTRITIONAL KETOSIS AND CLINICAL APPLICATIONS



THE OHIO STATE UNIVERSITY

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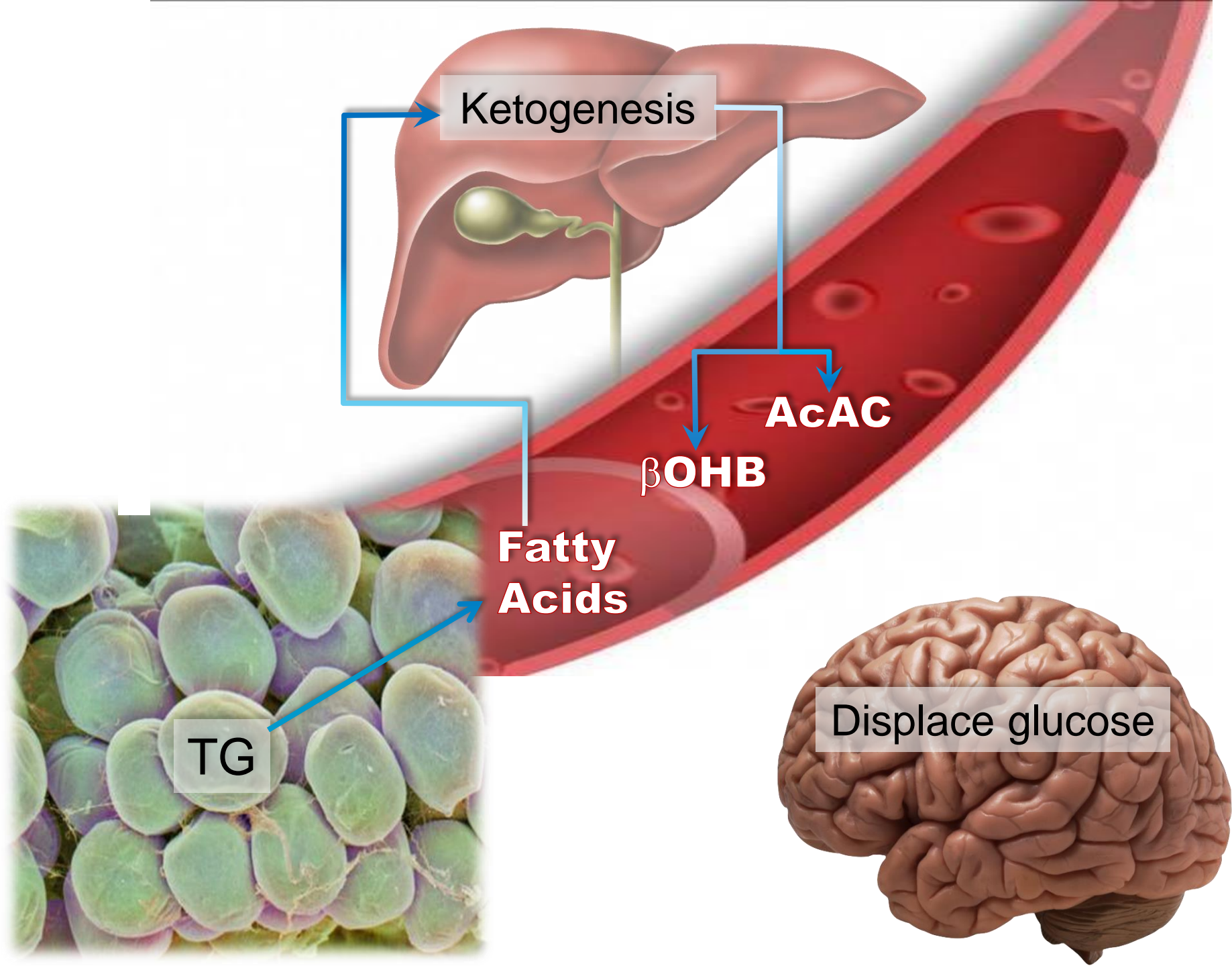
volek.1@osu.edu

LEARNING OBJECTIVES

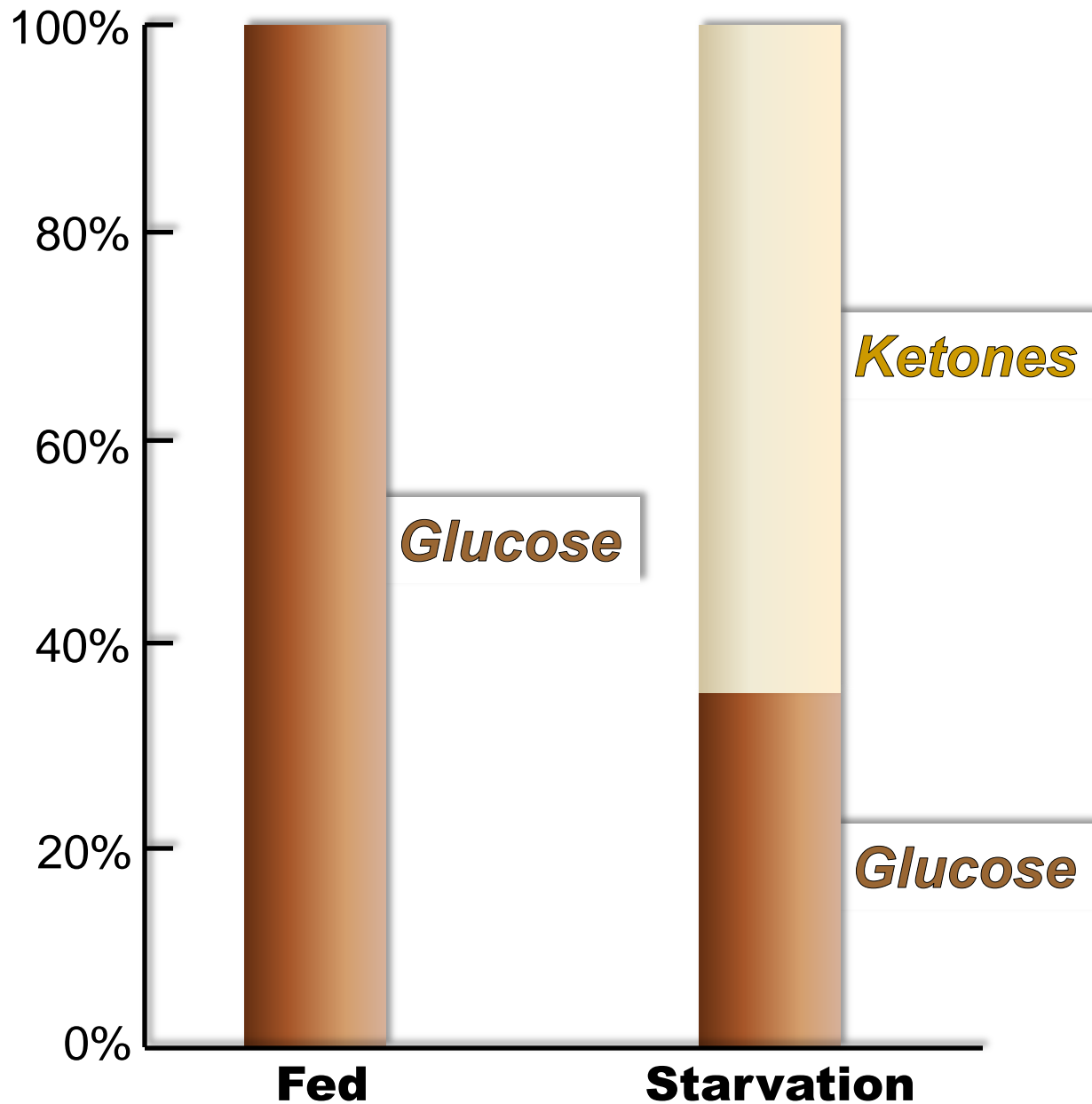
- 1. Review the concept of ketogenesis, nutritional ketosis, and keto-adaptation**
2. Discuss potential avenues for ketogenic diets in clinical practice
3. Learn about the potential for ketogenic approaches in exercise and physical performance

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



Ketones: a substitute for glucose



Ketone Terminology

Ketosis

Hepatically-derived energy containing substances derived from fatty acids that provide fuel to nearly every cell in the body

Nutritional Ketosis

Process of accelerating production of ketones through restriction of carbohydrate

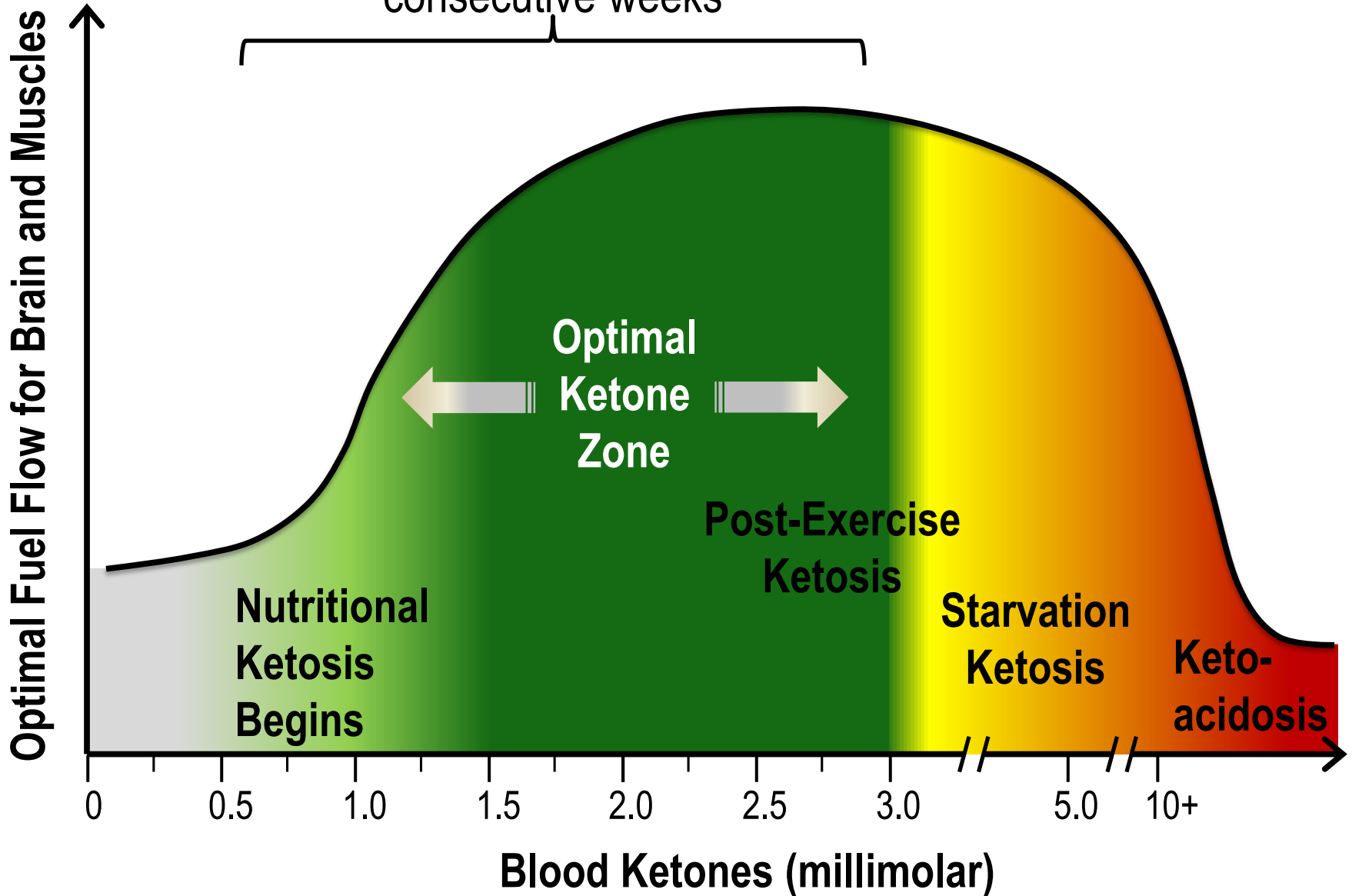
Keto-Acidosis

A dangerous side effect of Type I diabetes

Keto-Adaptation

A health-promoting process of shifting to using predominately fat

Keto-Adaptation happens
when you are in this zone over
consecutive weeks



Ketones are Signaling Molecules

Invited Review

β -hydroxybutyrate: Much more than a metabolite

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

^aDivision of Geriatrics, University of California San Francisco, San Francisco, CA, USA

^bGladstone Institutes, University of California San Francisco, 1650 Owens St., San Francisco, CA 94158, USA

A B S T R A C T

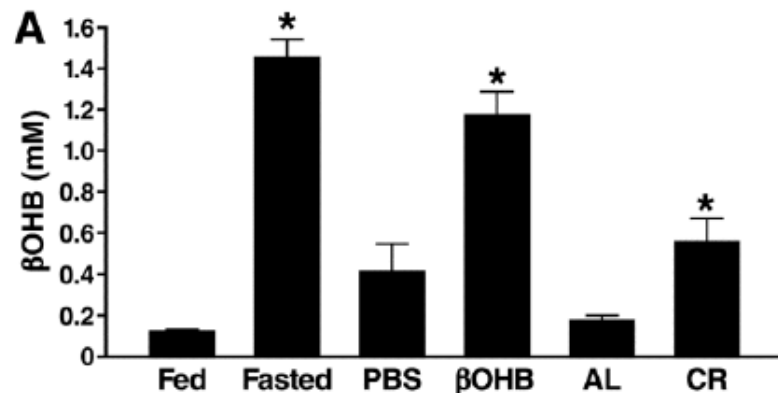
The ketone body β -hydroxybutyrate (β OHB) is a convenient carrier of energy from adipocytes to peripheral tissues during fasting or exercise. However, β OHB is more than just a metabolite, having important cellular signaling roles as well. β OHB is an endogenous inhibitor of histone deacetylases (HDACs) and a ligand for at least two cell surface receptors. In addition, the downstream products of β OHB metabolism including acetyl-CoA, succinyl-CoA, and NAD⁺ (nicotinamide adenine dinucleotide) themselves have signaling activities. These regulatory functions of β OHB serve to link the outside environment to cellular function and gene expression, and have important implications for the pathogenesis and treatment of metabolic diseases including type 2 diabetes.

Ketones are Signaling Molecules

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 Moan,³ Carrie A. Grueter,^{4,5} Hyungwook Lim,^{1,2} Laura R. Saunders,^{1,2} Robert D. Stevens,⁶ Christopher B. Newgard,⁶ Robert V. Farese Jr.,^{2,4,5} Rafael de Cabo,⁷ Scott Ulrich,⁸ Katerina Akassoglou,³ Eric Verdin^{1,2*}

6 December 2012 / Page 1/ 10.1126/science.1227166



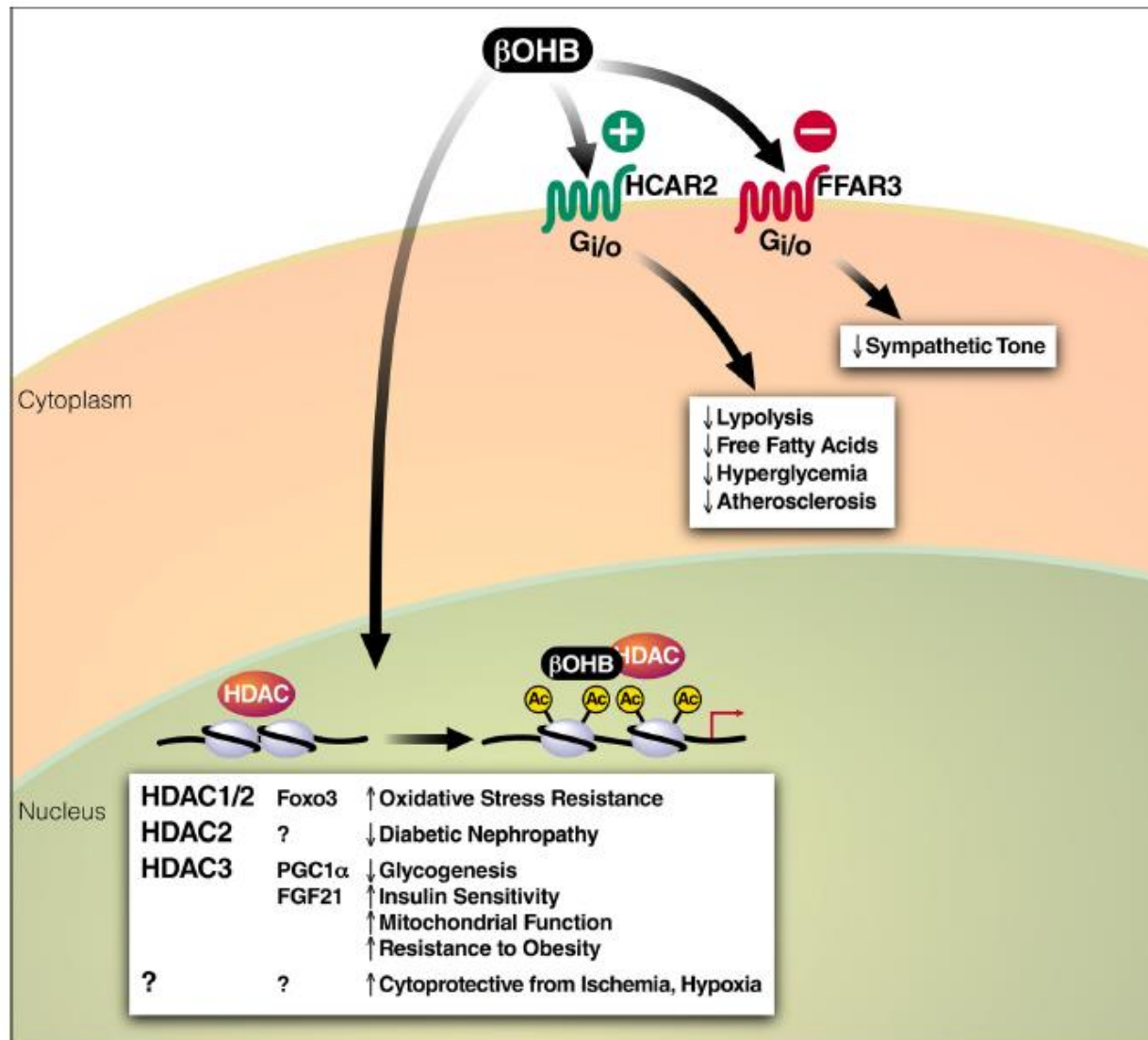
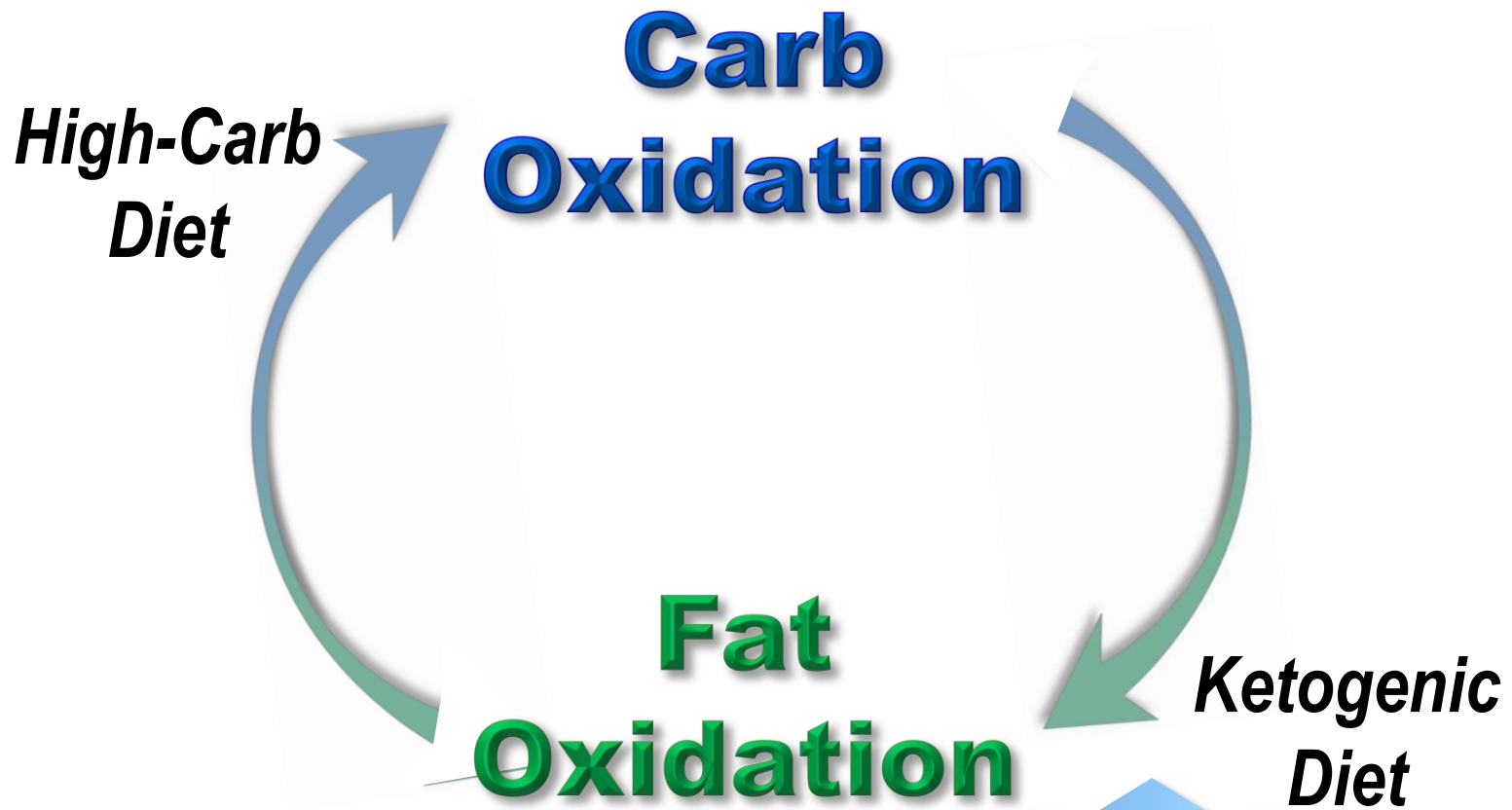


Fig. 1 – Cellular signaling functions of the ketone body β OHB. β OHB itself is an endogenous inhibitor of histone deacetylase enzymes, thereby altering gene expression to regulate resistance to oxidative stress and possibly many other cellular functions. β OHB is also a ligand for at least two cell-surface G-protein-coupled receptors that modulate lipolysis, sympathetic tone, and metabolic rate.

Keto-Adaptation

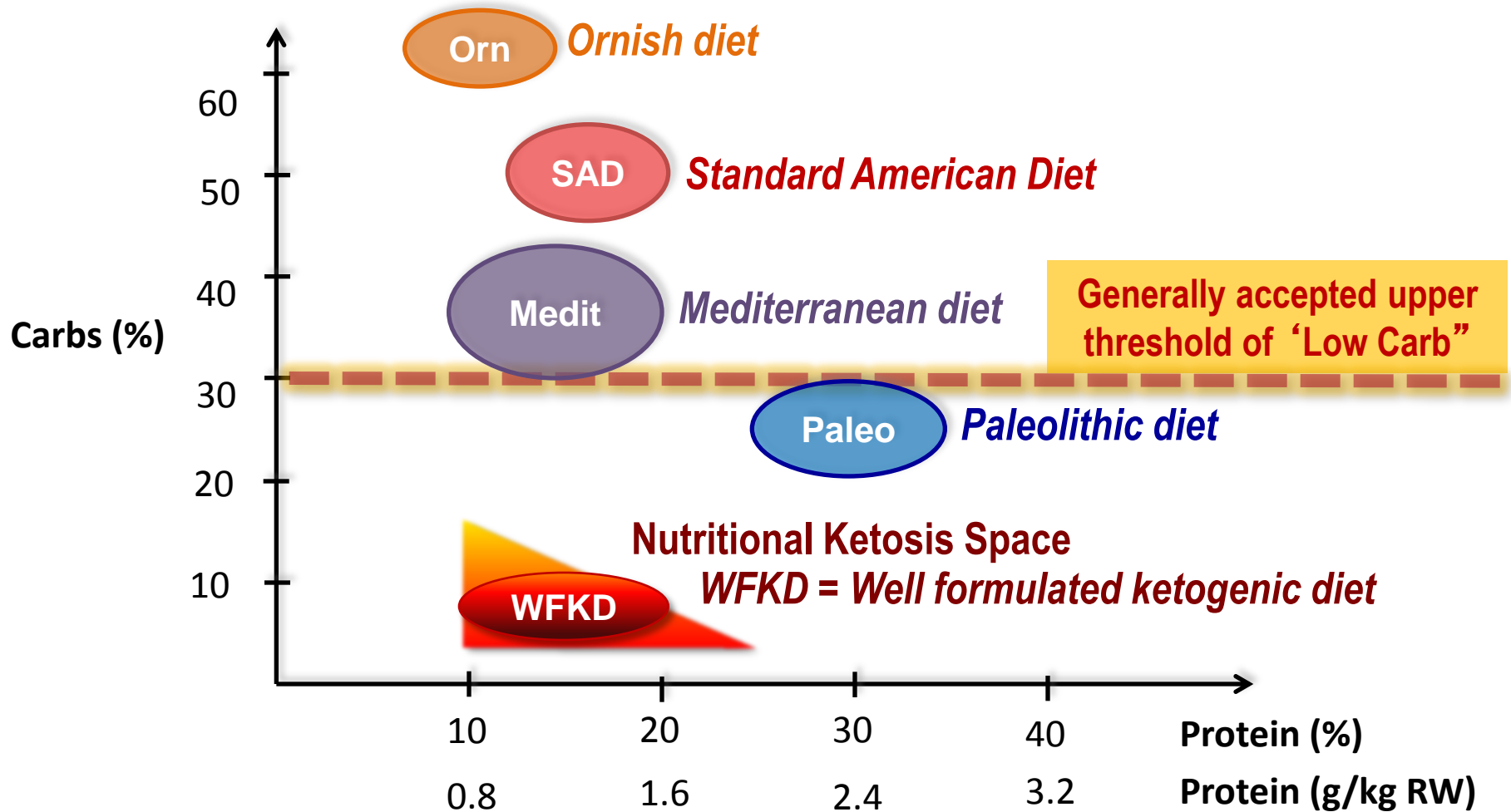
A metabolic blue print hard-wired into our genetic code that sustains optimum fuel flow to all organs (including the brain) through use of pathways humans have acquired >2 million years as hunters/gatherers/herders.



↑ **2x**

Enhanced fat oxidation facilitates weight loss & broad spectrum health benefits

Ketogenic Diets are Distinct from Other Popular Diet Approaches



Note: *Carbs (%) = Percent of dietary carbs relative to daily energy expenditure*
Protein (%) = Percent of dietary protein relative to daily energy expenditure
Protein (g/kg RW) = Grams of dietary protein relative to reference body weight



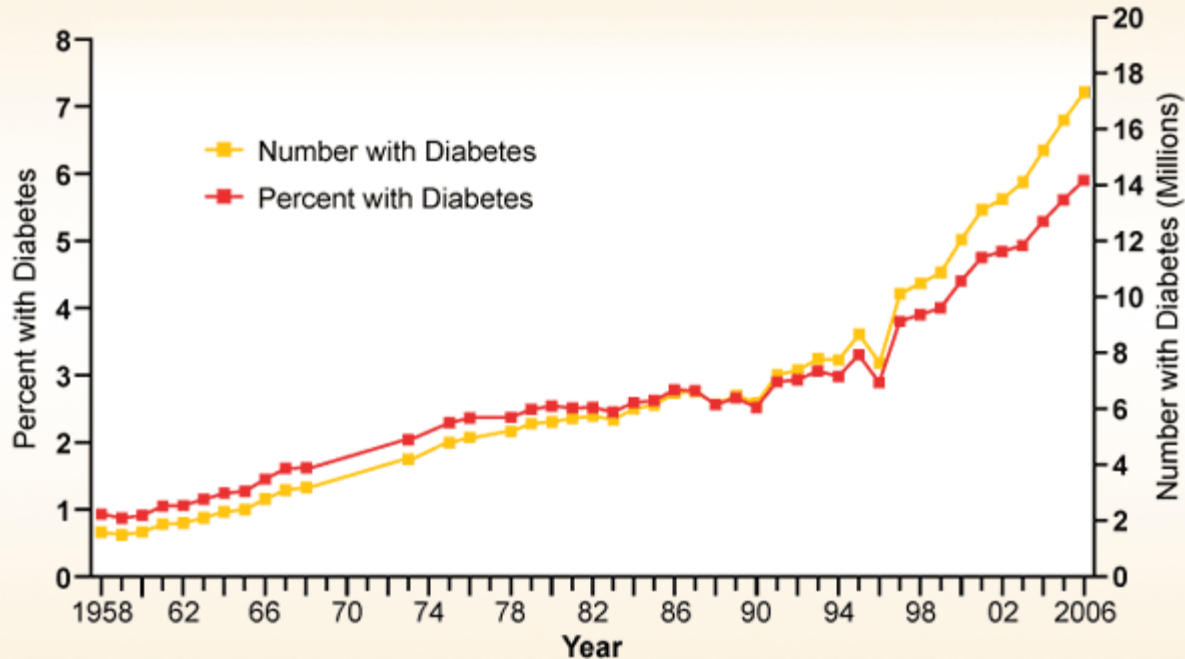
LEARNING OBJECTIVES

1. Review the concept of ketogenesis, nutritional ketosis, and keto-adaptation
- 2. Discuss potential avenues for ketogenic diets in clinical practice**
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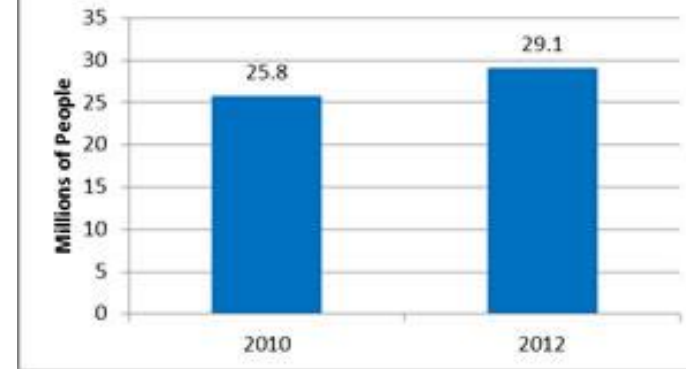
Diabetes is a Pandemic

The scientific consensus is such that diabetes is a chronic disease that is irreversible.

Number and Percentage of U.S. Population with Diagnosed Diabetes



American Population With Diabetes



1 in 4: Americans ≥ 65 yr w/ diabetes

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

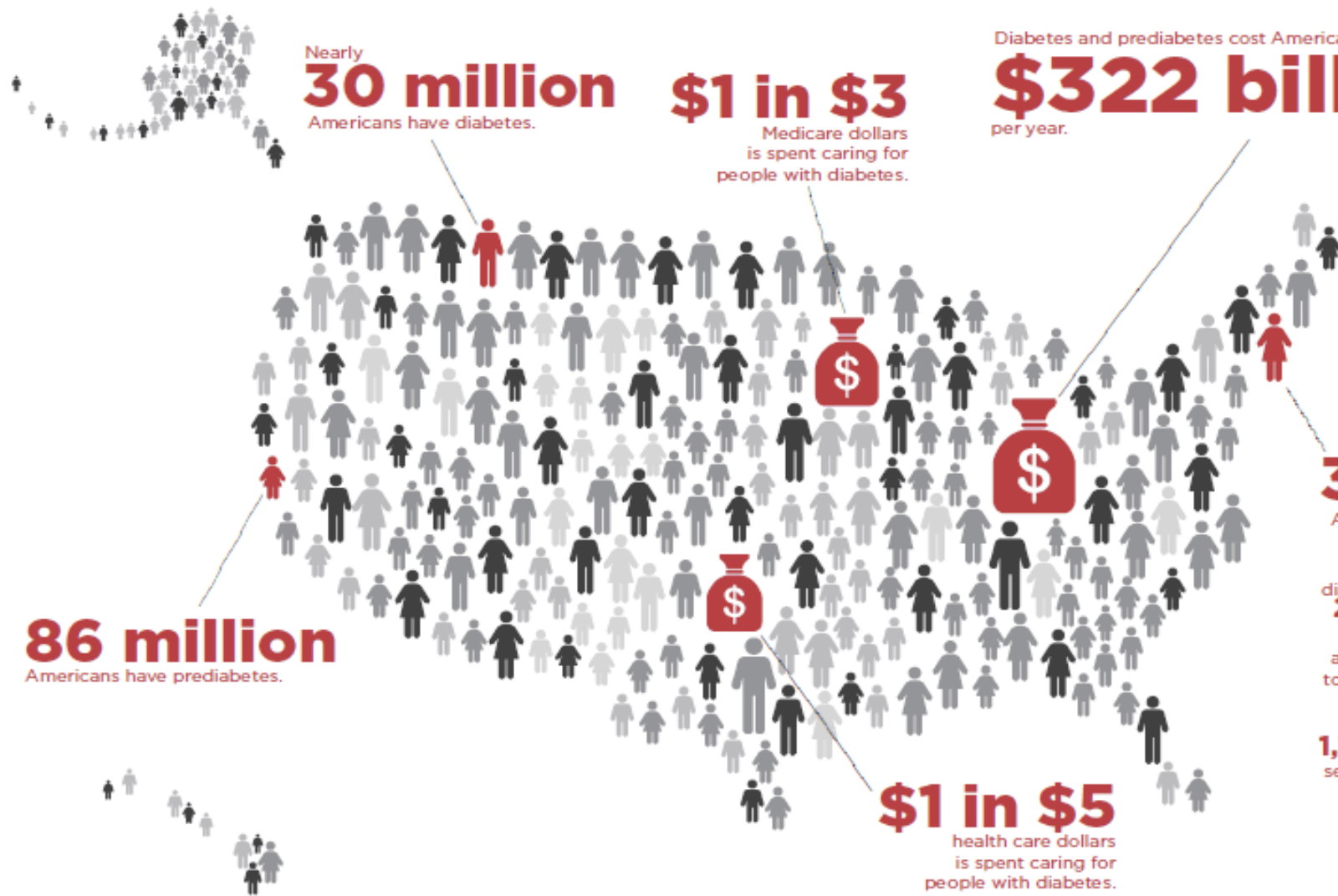
Americans have prediabetes.

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.



Drug & lifestyle treatments have had limited success in curtailing the obesity/diabetes epidemics

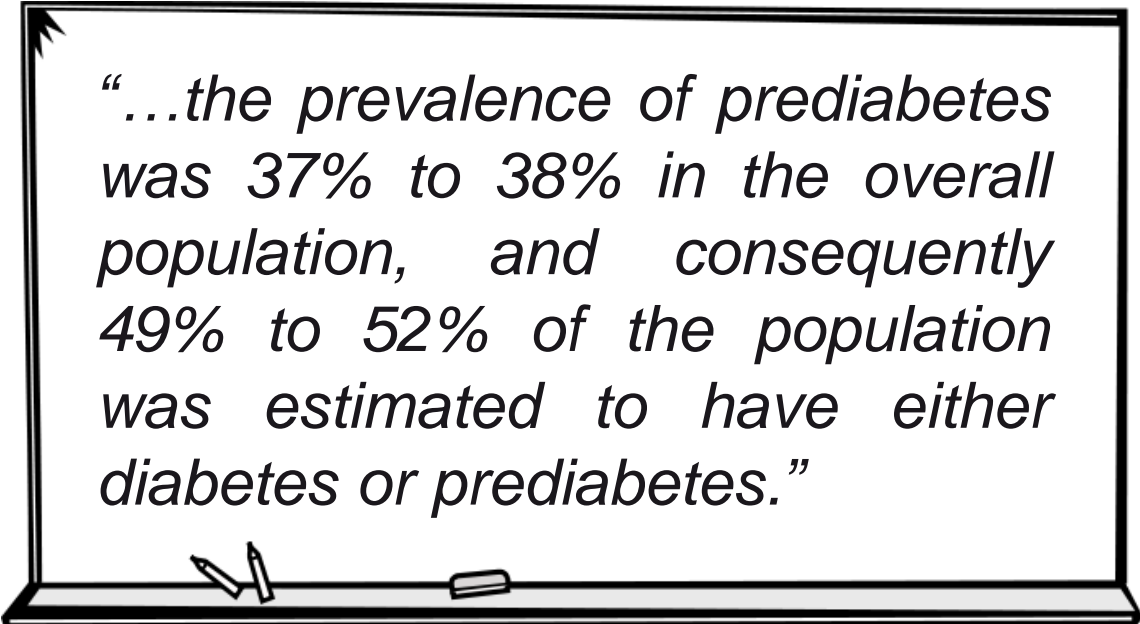
Research

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

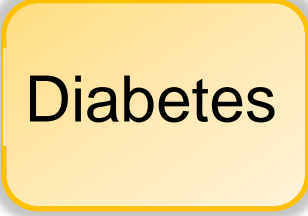
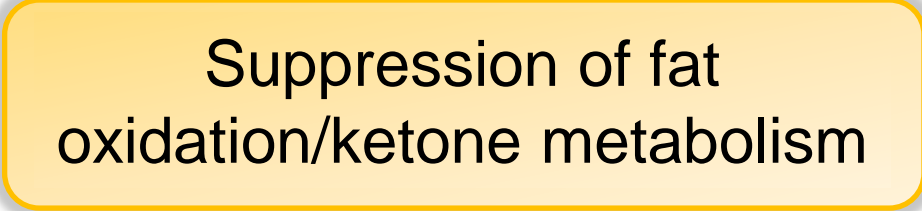
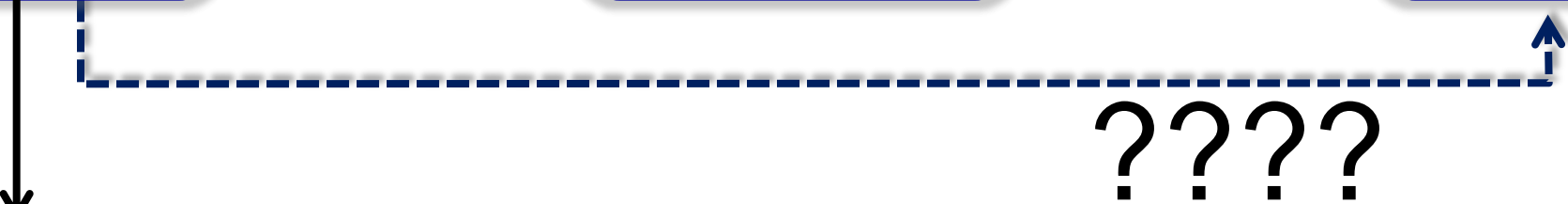
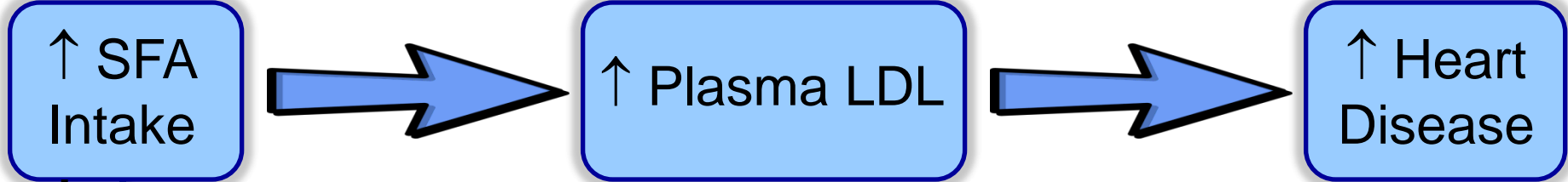
[JAMA. 2015;314\(10\):1021-1029. doi:10.1001/jama.2015.10029](https://doi.org/10.1001/jama.2015.10029)



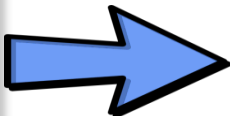
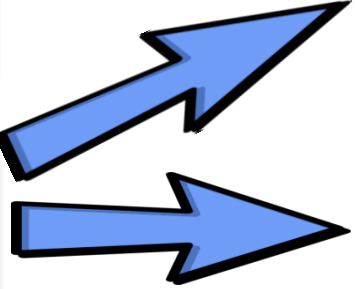
“...the prevalence of prediabetes was 37% to 38% in the overall population, and consequently 49% to 52% of the population was estimated to have either diabetes or prediabetes.”

Carbs or fat as primary driver of obesity/diabetes?

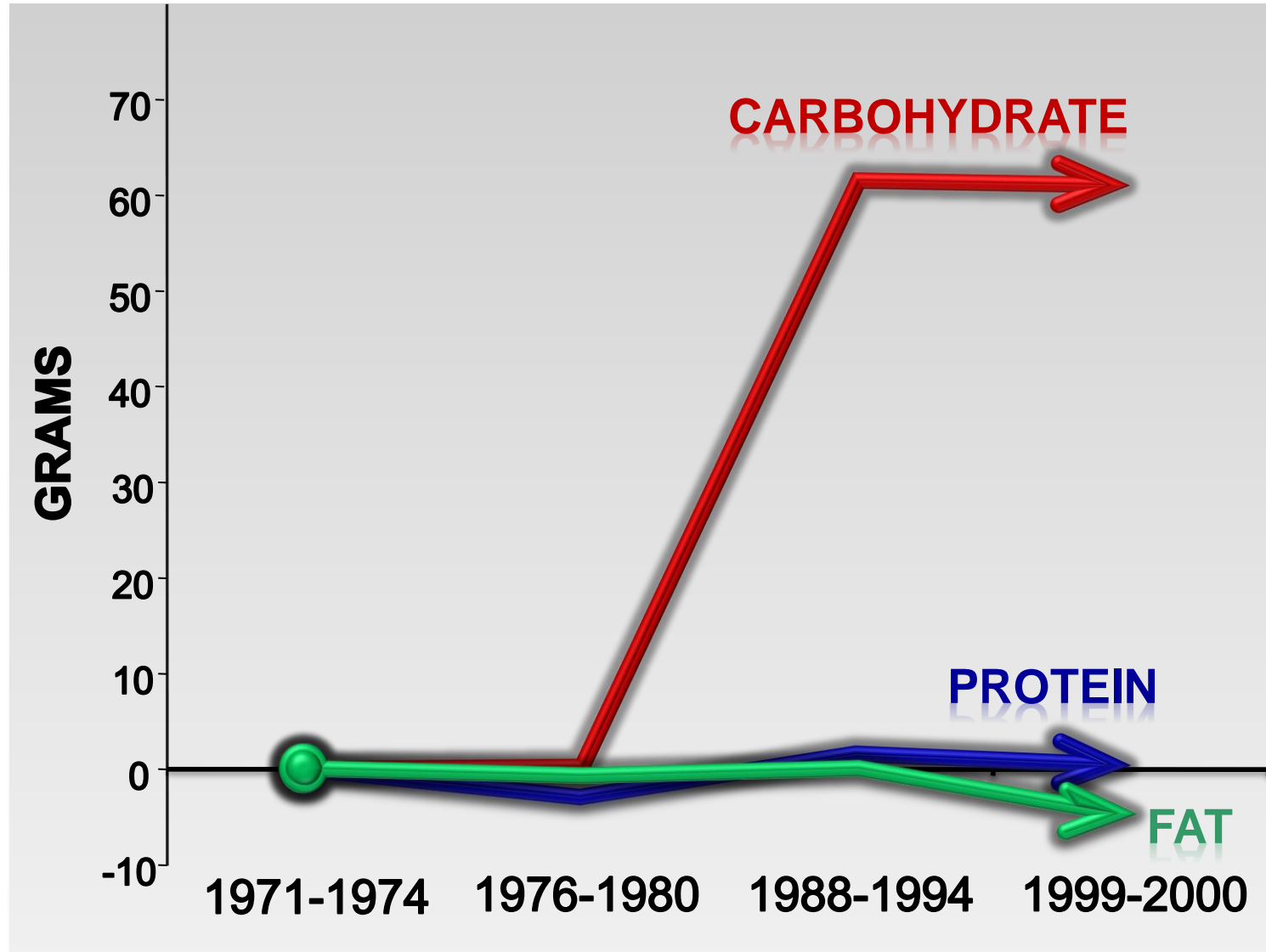
The Diet Heart Hypothesis



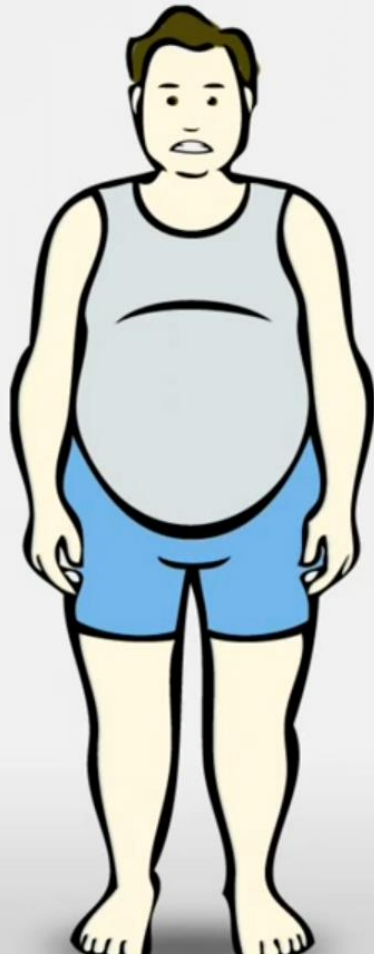
Poor Health



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



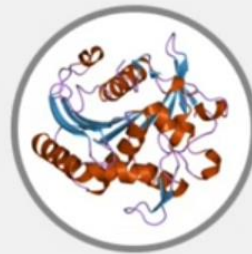
Eating too many carbs relative to our tolerance manifests in an insulin resistant phenotype



THE METABOLIC SYNDROME



HEART DISEASE



LIPID PROBLEMS



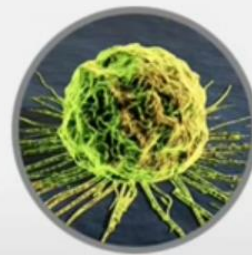
HYPERTENSION



TYPE 2 DIABETES



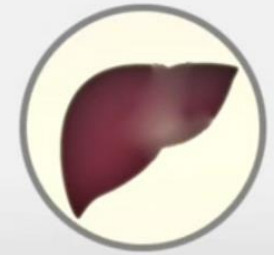
DEMENTIA



CANCER



POLYCYSTIC
OVARIAN
SYNDROME



NON-ALCOHOLIC
FATTY LIVER
DISEASE

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

Ubiquitous amounts of carbs is the predominant environmental pressure pushing us toward the insulin resistant phenotype; now over half the population.

← ↑Carbs ↓Carbs →

T2D

**Insulin
Resistant
Phenotype**

**Keto-
Adapted
Phenotype**

Disease ←

→ **Robust
Health**

Nutrition & Metabolism

Review

Open Access

Carbohydrate restriction improves the features of Metabolic Syndrome. Metabolic Syndrome may be defined by the response to carbohydrate restriction

Jeff S Volek¹ and Richard D Feinman^{*2}

Progress in Lipid Research 47 (2008) 307–318

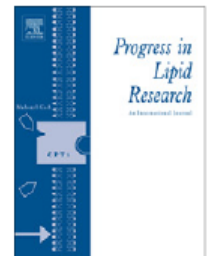


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Contents lists available at ScienceDirect

Progress in Lipid Research

journal homepage: www.elsevier.com/locate/plipres

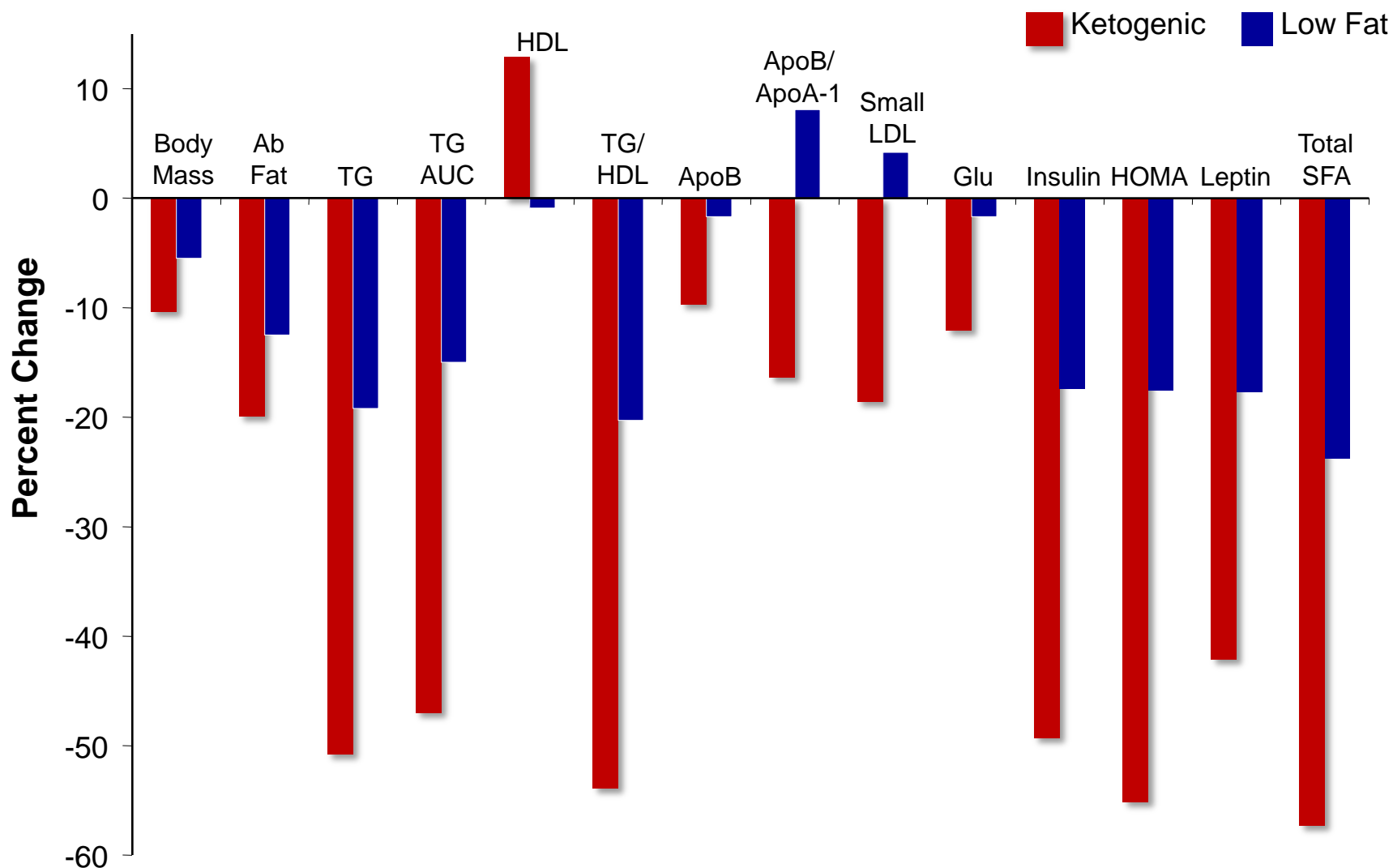


Review

Dietary carbohydrate restriction induces a unique metabolic state positively affecting atherogenic dyslipidemia, fatty acid partitioning, and metabolic syndrome

Jeff S. Volek^{a,*}, Maria Luz Fernandez^b, Richard D. Feinman^c, Stephen D. Phinney^d

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).

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 McKenzie¹, PhD; Sarah J Hallberg^{1,2}, DO, MS; Brent C Creighton¹, PhD; Brittanie M Volk¹, RD, PhD; Theresa M Link¹, RD, CDE; Marcy K Abner¹, RD; Roberta M Glon¹, RN, BSN; James P McCarter¹, MD, PhD; Jeff S Volek¹, RD, PhD; Stephen D Phinney¹, MD, PhD

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

CLINICAL TRIAL

Patients

N = 378

262 with type 2 diabetes
(T2D)

116 with pre-diabetes

Location

Greater Lafayette, Indiana

T2D Mean

Characteristics

Starting age: 54 yrs

Starting BMI: 41 kg/m²

Starting weight: 257 lbs
(117 kg)

67% female



Key Results

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

1.0 Average reduction in HbA1c (from 7.6 to 6.6)

87% Eliminated or reduced insulin

56% Reduced HbA1c < 6.5*

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

91% Completed Virta protocol

20% Average reduction in triglycerides

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

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.^{a,*}, C.J. Segal-Isaacson Ed.D., R.D.^b, Richard D. Feinman Ph.D.^c,

Type-2 Diabetes

Reversal of Diabetic Nephropathy by a Ketogenic Diet

Michal M. Poplawski¹, Jason W. Mastaitis², Fumiko Isoda¹, Fabrizio Grosjean³, Feng Zheng³, Charles V.

Type-1 Diabetes

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

Jorgen Vesti Nielsen^{1*}, Caroline Gando², Eva Joensson³ and Carina Paulsson²

Autism

Potential therapeutic use of the ketogenic diet in autism spectrum disorders

Eleonora Napoli^{1*}, Nadia Dueñas¹ and Cecilia Giulivi^{1,2}

Polycystic Ovary Syndrome (PCOS)

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

John C Mavropoulos¹, William S Yancy^{1,2}, Juanita Hepburn¹ 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^a, Christian Bergman^a, Jong-Hwan Lee^b, Ruiqian Wan^c, M. Todd King^a,

Epilepsy

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

Meta-analysis

Hai-feng Li¹, MM; Yan Zou², MPH; Gangqiang Ding², MD

Hypertension/Vascular Function

Dietary carbohydrate restriction improves insulin sensitivity, blood pressure, microvascular function, and cellular adhesion markers in individuals taking statins[☆]

Kevin D. Ballard^a, Erin E. Quann^a, Brian R. Kupchak^a, Brittanie M. Volk^a,

Parkinson Disease

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

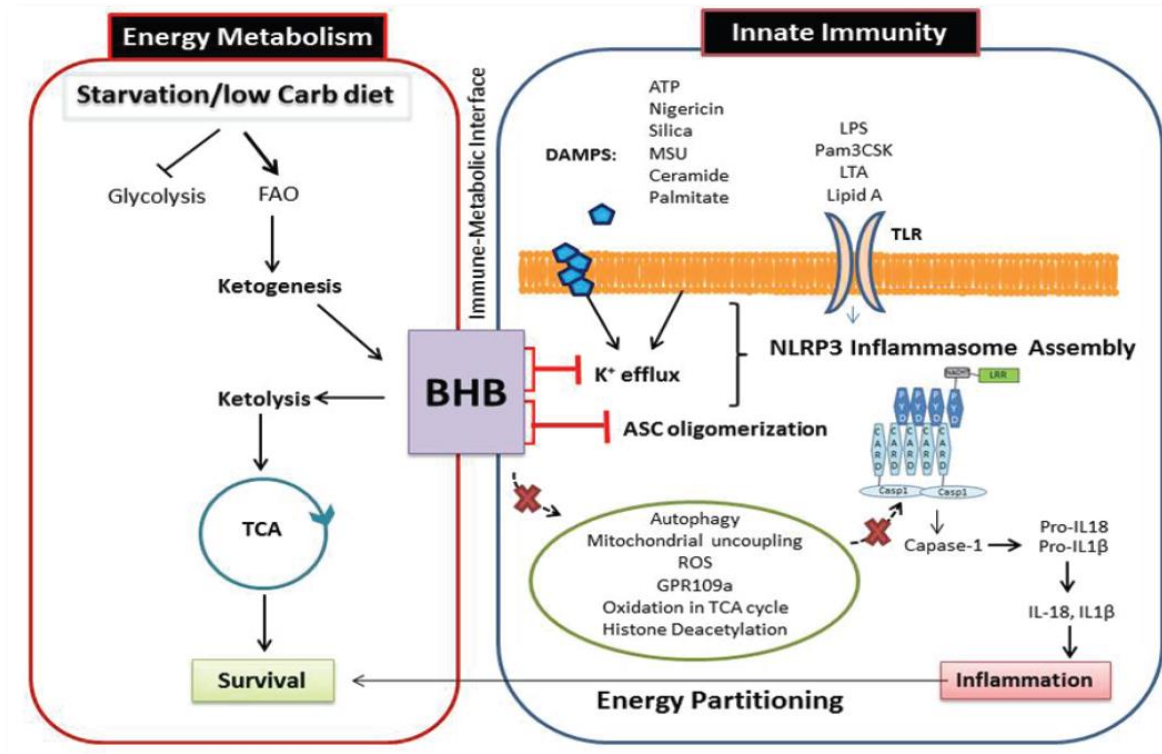
T. B. VanItallie, C. Nonas, A. Di Rocco, K. Boyar, K. Hyams and S. B. Heymsfield

Ketones decrease inflammation/oxidative stress

nature
medicine

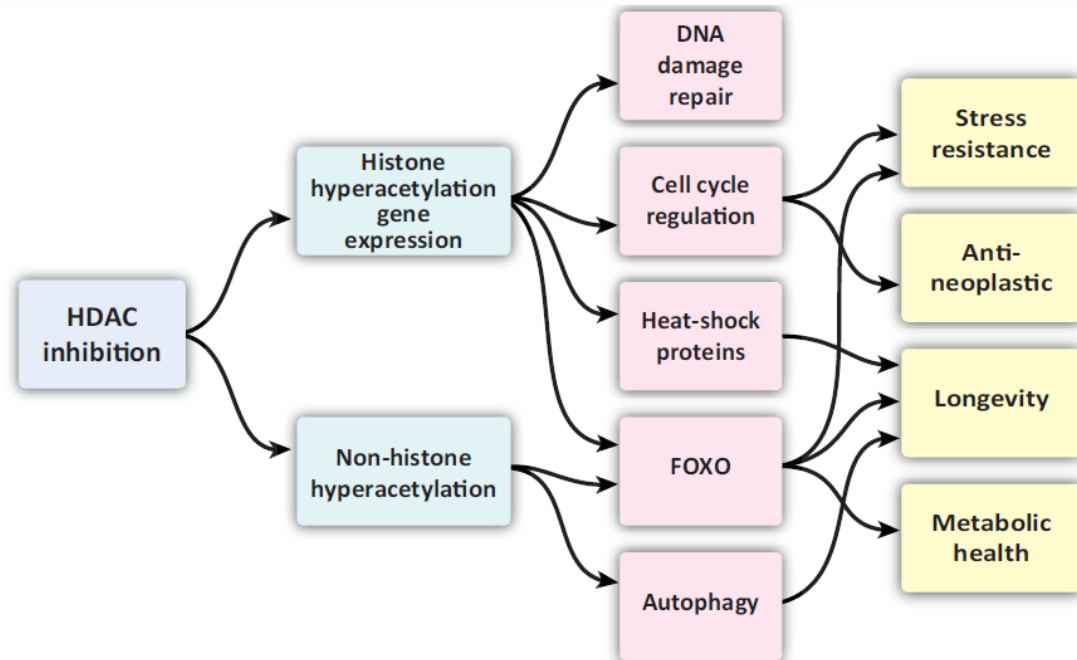
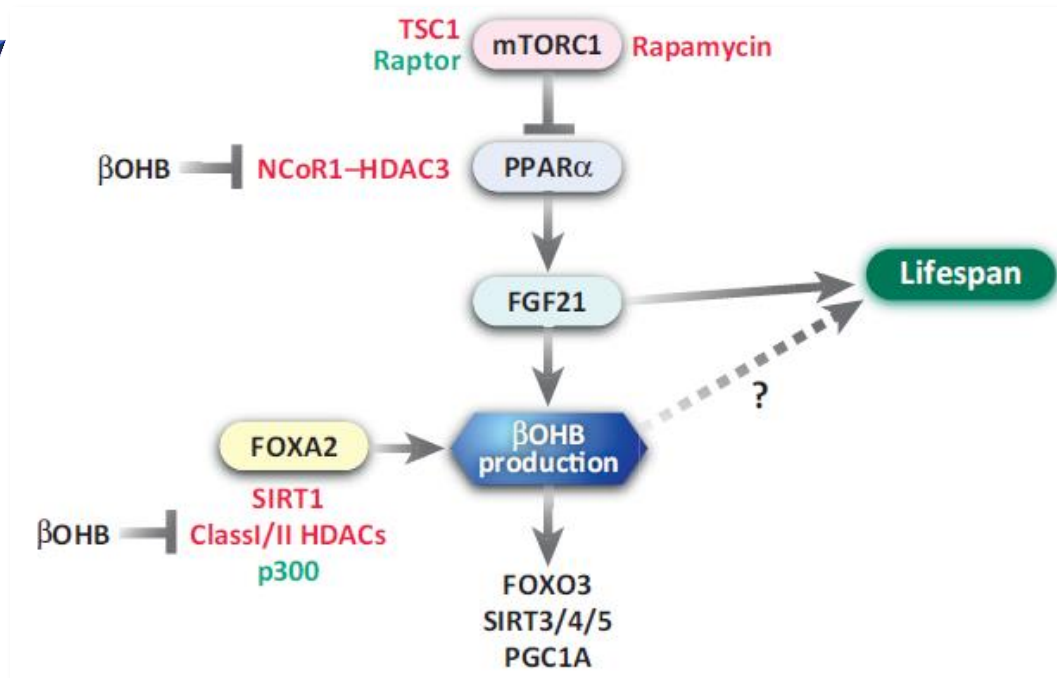
The ketone metabolite β -hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease

Yun-Hee Youm^{1,11}, Kim Y Nguyen^{1,11}, Ryan W Grant², Emily L Goldberg¹, Monica Bodogai³, Dongin Kim⁴, Dominic D'Agostino⁵, Noah Planavsky⁶, Christopher Lupfer⁷, Thirumala D Kanneganti⁷, Seokwon Kang⁸, Tamas L Horvath¹, Tarek M Fahmy⁴, Peter A Crawford⁹, Arya Biragyn³, Emad Alnemri⁸ & Vishwa Deep Dixit^{1,10}

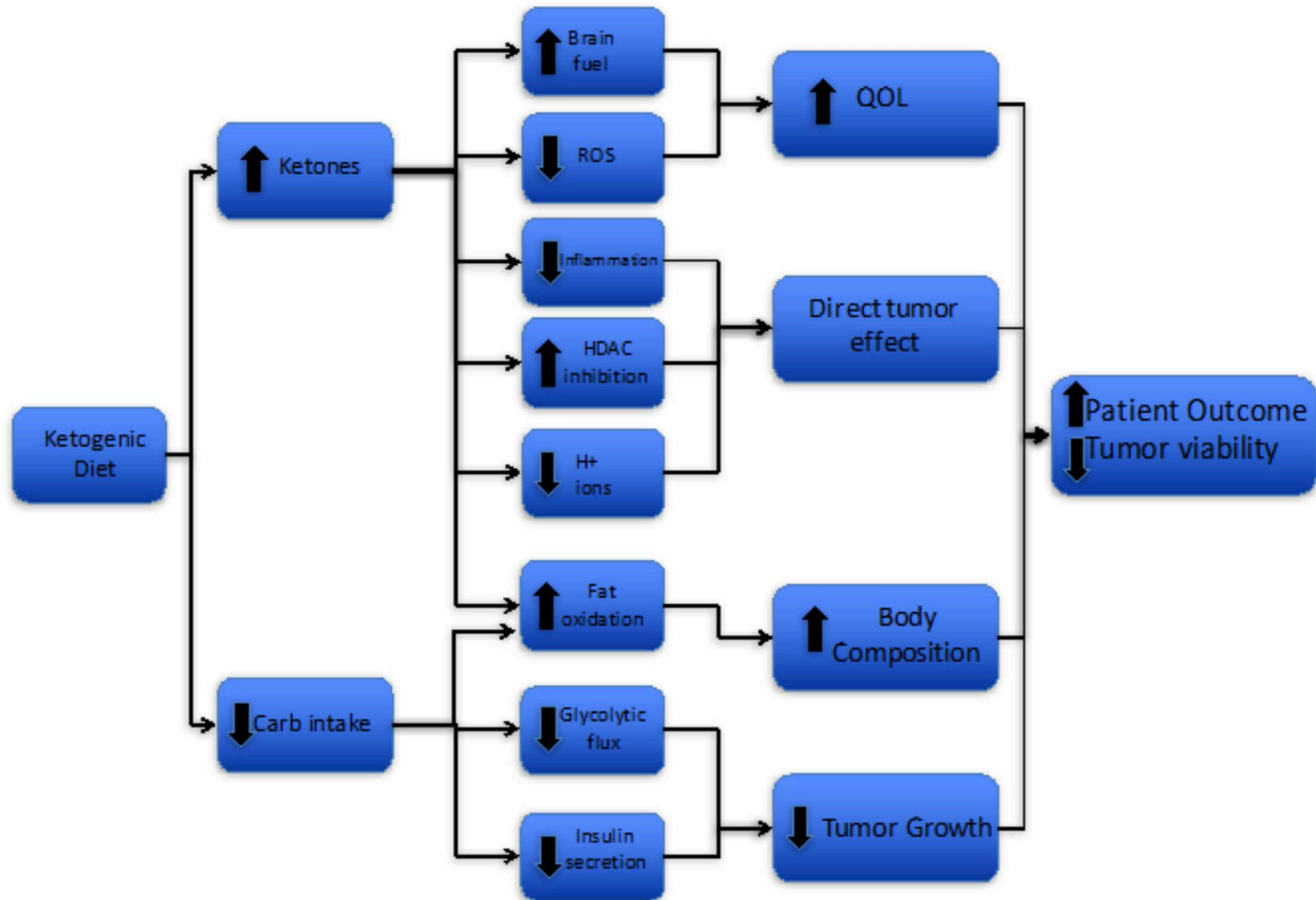


Ketones & Longevity

- Less stimulation of insulin, its receptor, and signaling pathways
- Less generation of reactive oxygen species (ROS)
- Endogenous inhibitor of HDACs
- Increased antioxidant defense
- Greater efficiency in providing cellular energy



Ketones & Cancer



Ketones & Cardiac Benefits

Ketones Step to the Plate

A Game Changer for Metabolic Remodeling in Heart Failure?

Stephen C. Kolwicz, Jr, PhD; Sophia Airhart, MD; Rong Tian, MD, PhD

The Failing Heart Relies on Ketone Bodies as a Fuel

Gregory Aubert, MD, PhD*; Ola J. Martin, PhD*; Julie L. Horton, MS; Ling Lai, MD, PhD;
Rick B. Vega, PhD; Teresa C. Leone, BS; Timothy Koves, PhD; Stephen J. Gardell, PhD;
Marcus Krüger, PhD; Charles L. Hoppel, MD; E. Douglas Lewandowski, PhD;
Peter A. Crawford, MD, PhD; Deborah M. Muoio, PhD; Daniel P. Kelly, MD

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Recent Ultra-Endurance Records By Low-Carb Athletes

Tim Olsen Wins
2012 Western States 100



Zach Bitter
American 100 Mile Track
Record Holder (11:47:21)



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



GREAT NEWS FOR LCHF: FIRST AND SECOND PLACE RIDERS OF THE TOUR DE FRANCE ARE LOW-CARB ADVOCATES!

📅 28 JULY 2016 📈 4105 SHARES

f SHARE

4102

TWEET

0

g+ +1

3

Great news for LCHF is that the first and second place riders of the Tour de France are both low-carb advocates!

David Grech said, “This year’s Tour de France was brilliant for the Low-Carb world. We have [Chris Froome](#) winning on a Real Food Lifestyle that appears, is incorporating low-carb healthy-fat strategies in his periods of training and recovery.

We also had Romain Bardet who after the final rest day was in 4th or 5th position and rode himself into outright second place by winning stage 19 of the Tour.



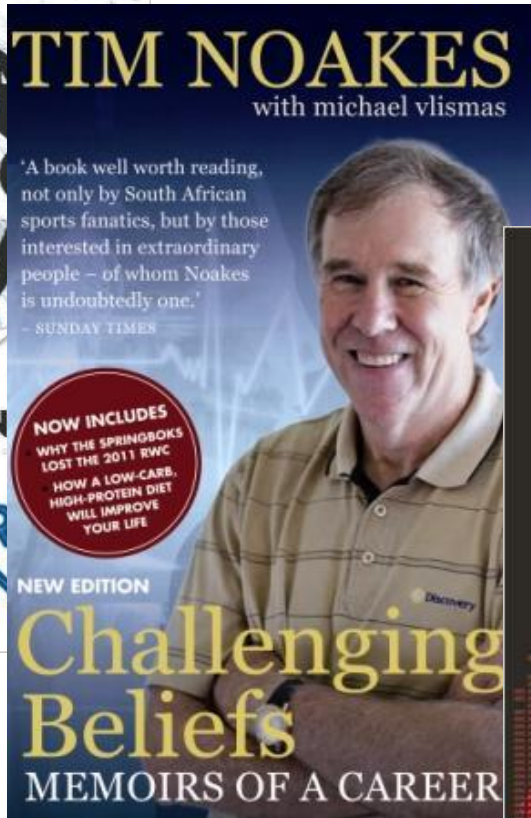
Froome in 2015 and 2009. When he turned pro in 2007 he weighed 167 pounds. In his 3 Tour de France victories — 2013, 2015, & 2016 — he has weighed as little as 145 lbs.

Jeff S. Volek, PhD, RD
Stephen D. Phinney, MD, PhD



THE ART AND SCIENCE OF
LOW CARBOHYDRATE
PERFORMANCE

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TIM NOAKES
with michael vlismas

'A book well worth reading, not only by South African sports fanatics, but by those interested in extraordinary people - of whom Noakes is undoubtedly one.'

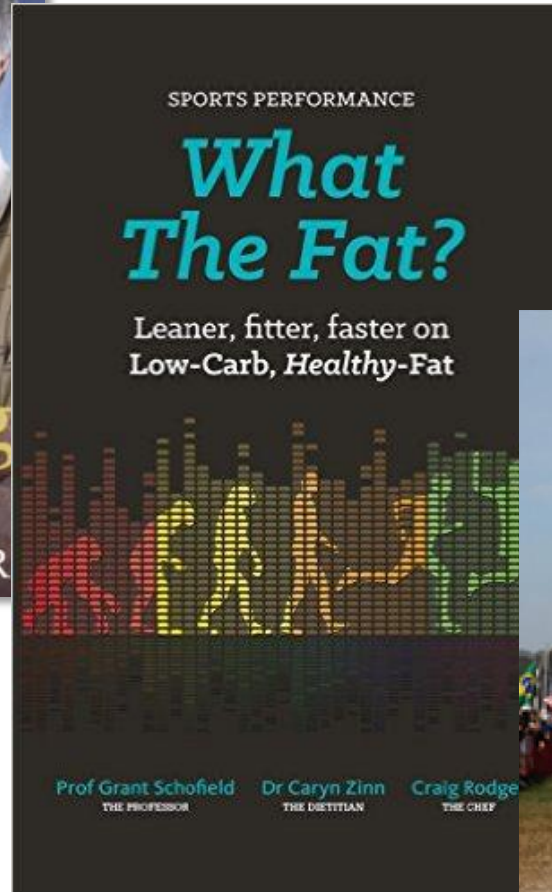
- SUNDAY TIMES

NOW INCLUDES
WHY THE SPRINGBOKS
LOST THE 2011 RWC
HOW A LOW-CARB,
HIGH-PROTEIN DIET
WILL IMPROVE
YOUR LIFE

NEW EDITION

Challenging Beliefs
MEMOIRS OF A CAREER

Debunking the High-Carbohydrate Dogma



SPORTS PERFORMANCE

What The Fat?

Leaner, fitter, faster on
Low-Carb, Healthy-Fat

Prof Grant Schofield THE PROFESSOR
Dr Caryn Zinn THE DIETITIAN
Craig Rodge THE CHEF



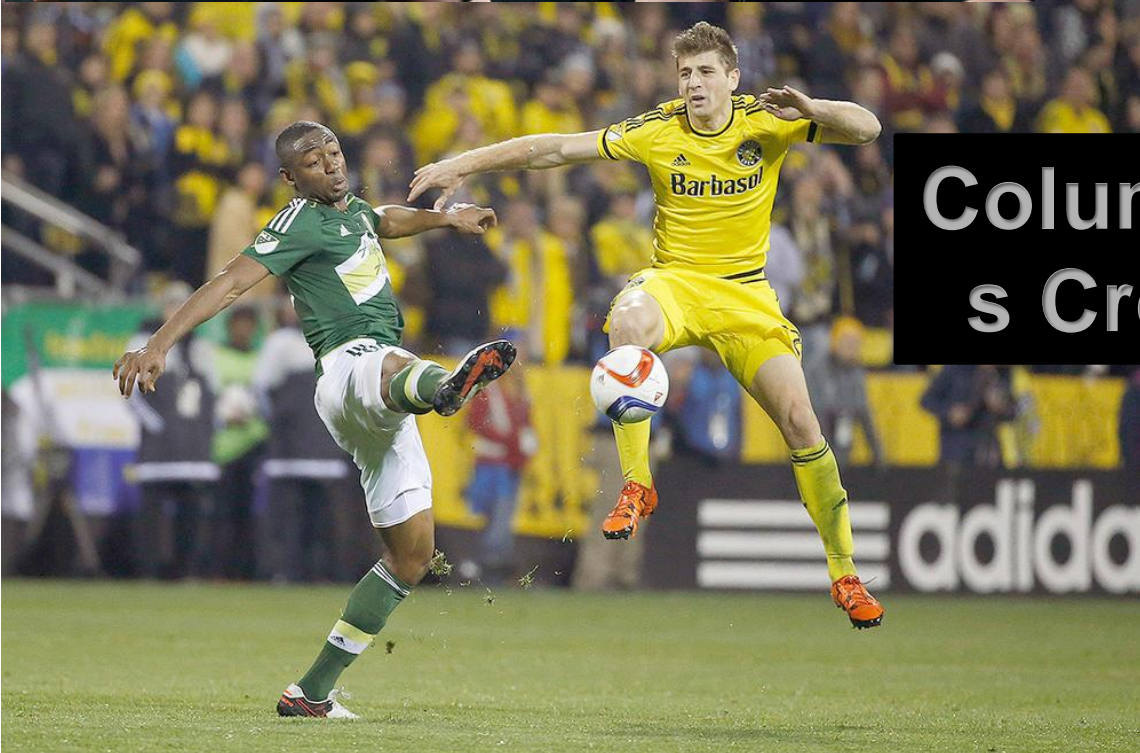
CARB LOADING JUST HIT THE WALL

RUN ON FAT
CEREAL KILLERS 2

WWW.CEREALKILLERSMOVIE.COM
- COMING SOON -



All
Blacks



Columbu
s Crew



Faster Study

Fat Adapted Substrate Oxidation in Trained Elite Runners

METABOLISM CLINICAL AND EXPERIMENTAL 65 (2016) 100–110

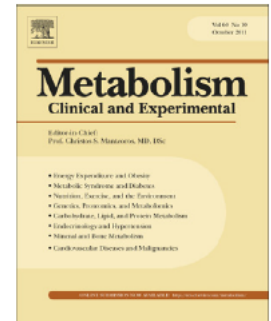


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Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com



Metabolic characteristics of keto-adapted ultra-endurance runners



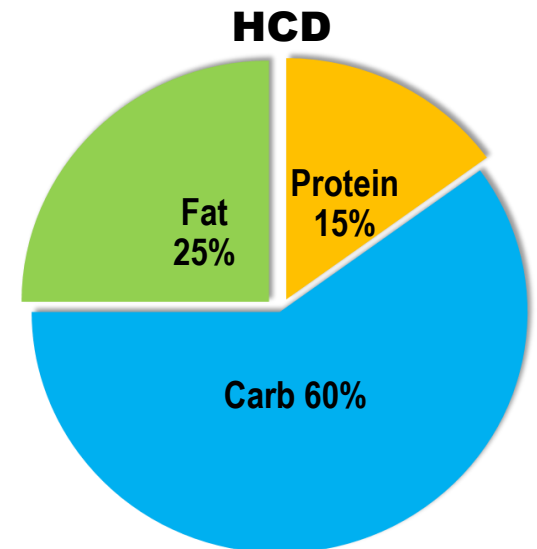
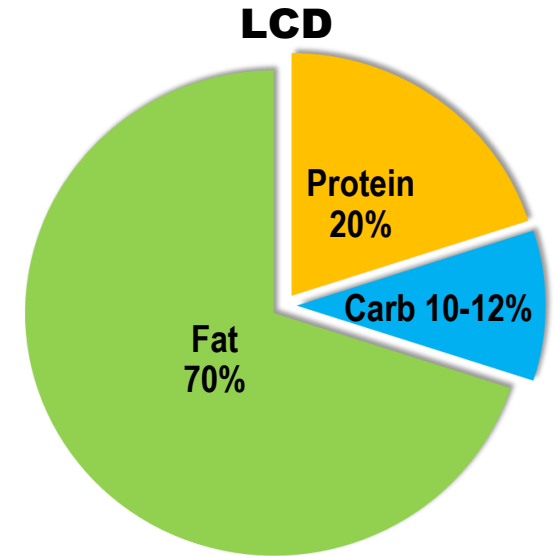
Jeff S. Volek^{a,b,*}, Daniel J. Freidenreich^{a,b}, Catherine Saenz^{a,b}, Laura J. Kunces^a, Brent C. Creighton^a, Jenna M. Bartley^a, Patrick M. Davitt^a, Colleen X. Munoz^a, Jeffrey M. Anderson^a, Carl M. Maresh^{a,b}, Elaine C. Lee^a, Mark D. Schuenke^c, Giselle Aerni^a, William J. Kraemer^{a,b}, Stephen D. Phinney^d

Aim

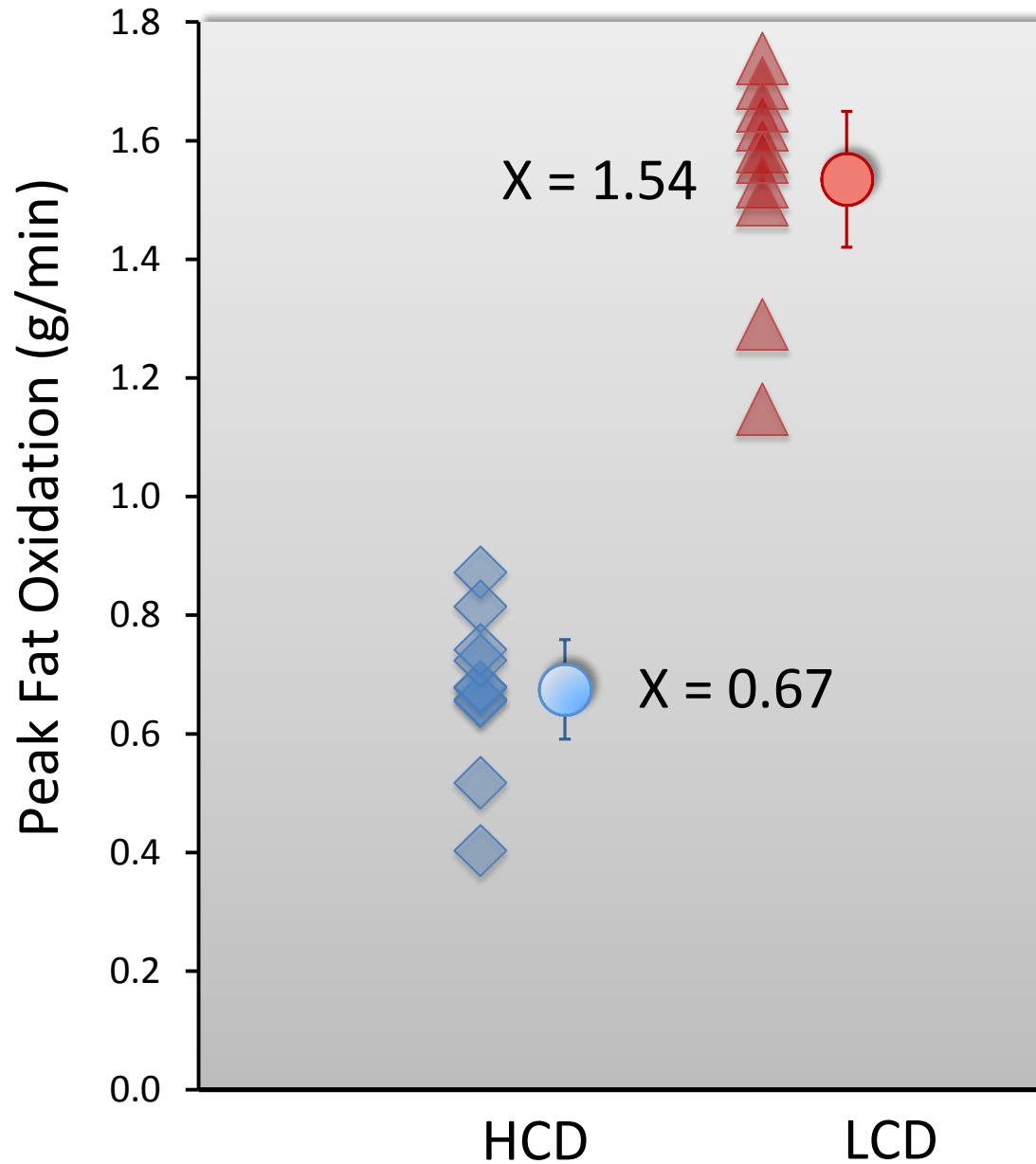
Take a deeper look into the keto-adapted athlete



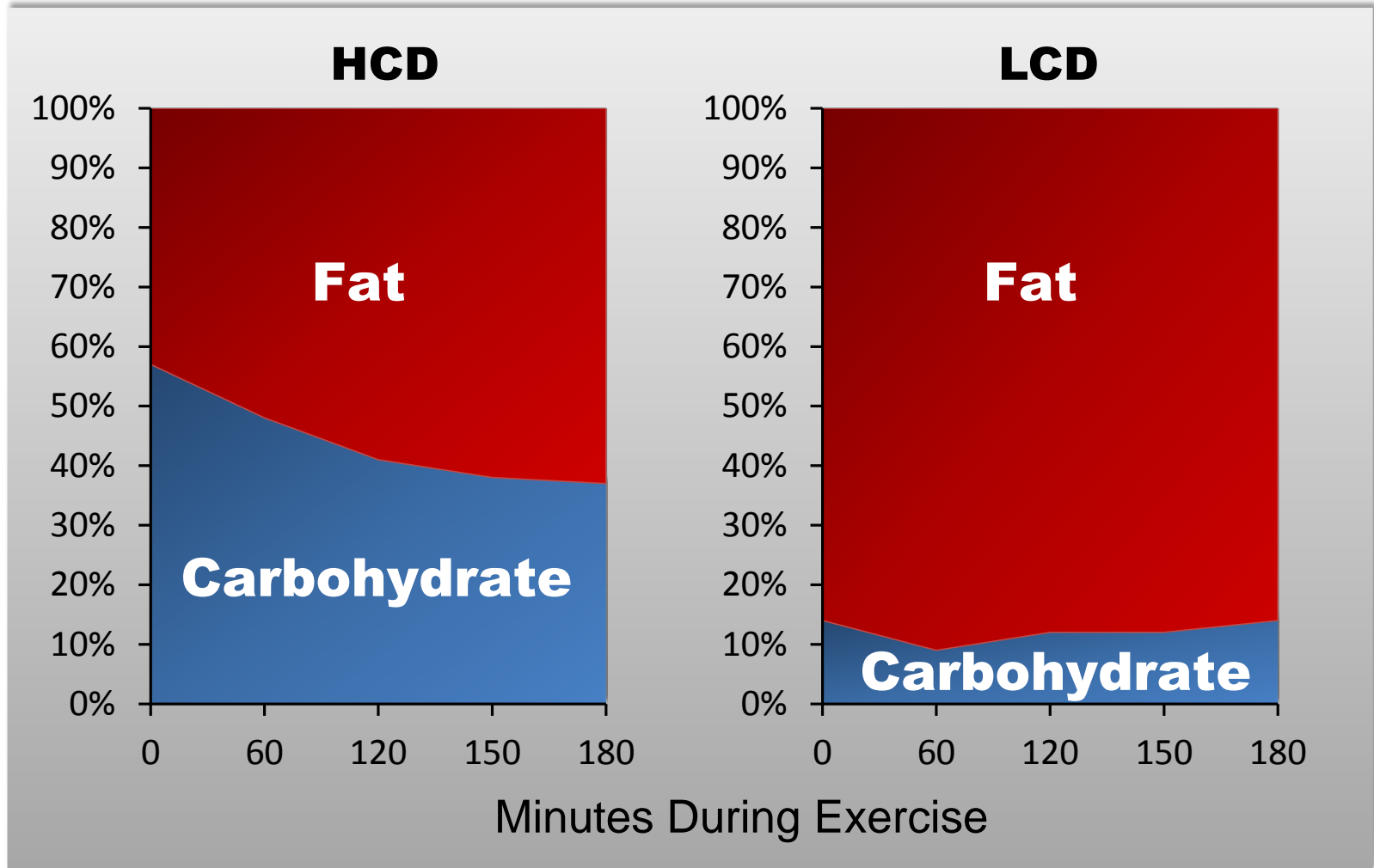
	HCD (n = 10)		LCD (n = 10)	
	Mean	Range	Mean	Range
Age (yr)	33	22 - 40	34	21 - 45
Height (cm)	173.9	167.1 - 182.0	175.7	165.1 - 189.4
Body mass (kg)	66.5	57.9 - 79.9	68.8	55.5 - 81.6
Body fat (%)	9.6	4.7 - 15.5	7.8	4.5 - 12.3
Fat mass (g)	6,513	2,774 - 12,102	5,454	2,953 - 8,780
Lean mass (kg)	57.3	49.4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



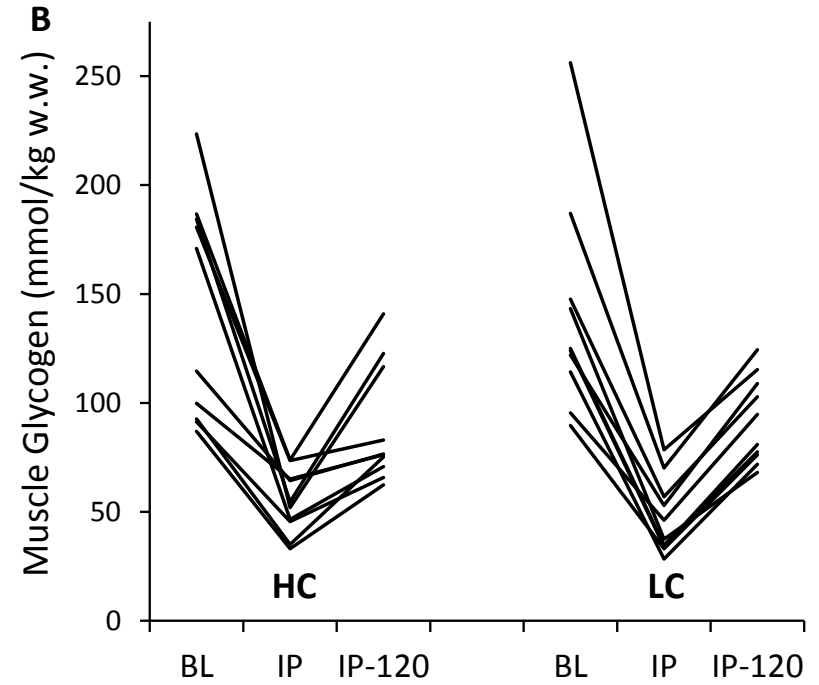
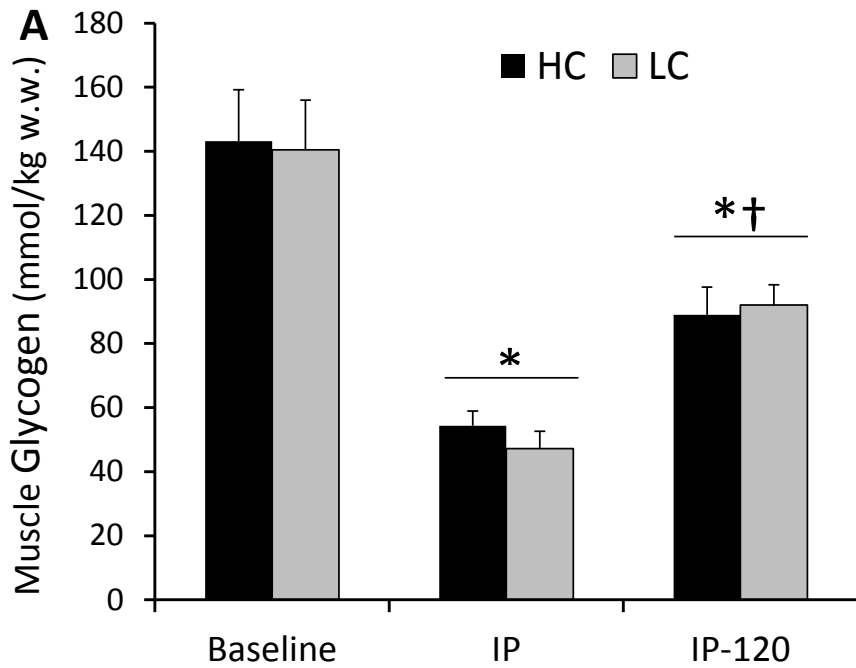
Peak Fat Burning



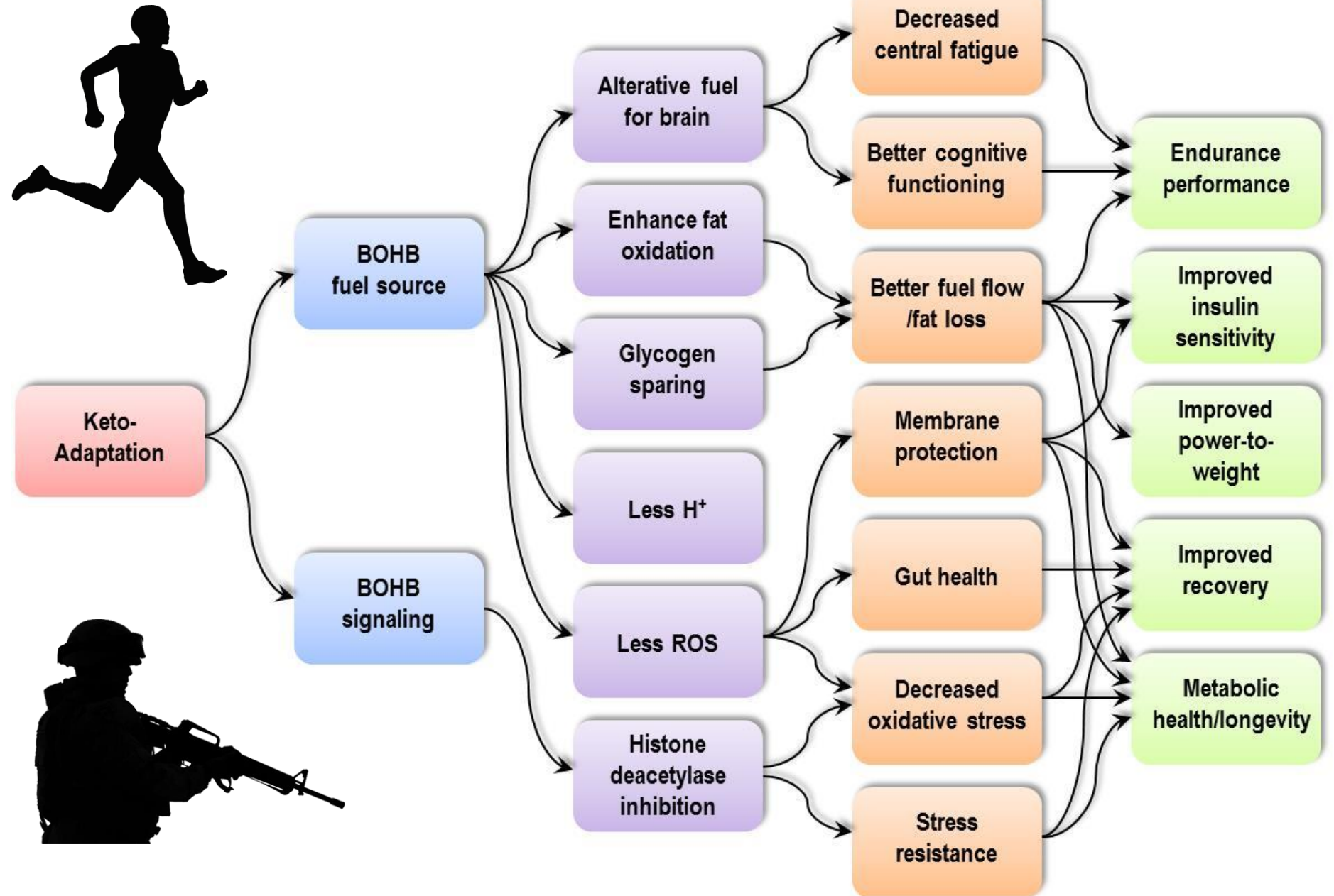
Fuel Use During Submaximal Exercise



Muscle Glycogen



The Keto-Adapted Phenotype



SUMMARY

- 1. Ketosis & keto-adaption are natural, if not preferred, metabolic states for humans**
- 2. Sustained restriction of carbs to achieve nutritional ketosis results in a shift from an insulin-resistant (unhealthy) to a keto-adapted (healthy) phenotype**
- 3. Because it gets at the root cause, keto-adaptation has broad applications for managing disease & promoting health**