The Ketogenic Diet:

Efficacy, Safety, and Utility as a Weight Loss Tool

Dr. John Allen

2/1/2019

Disclosures

Objectives

1. *Identify Clinical Relevance*
2. *Define the Physiology of the Ketogenic Diet*
3. *Explore Efficacy and Safety of the Ketogenic Diet*
4. *Determine the Clinical Utility of the Ketogenic Diet*

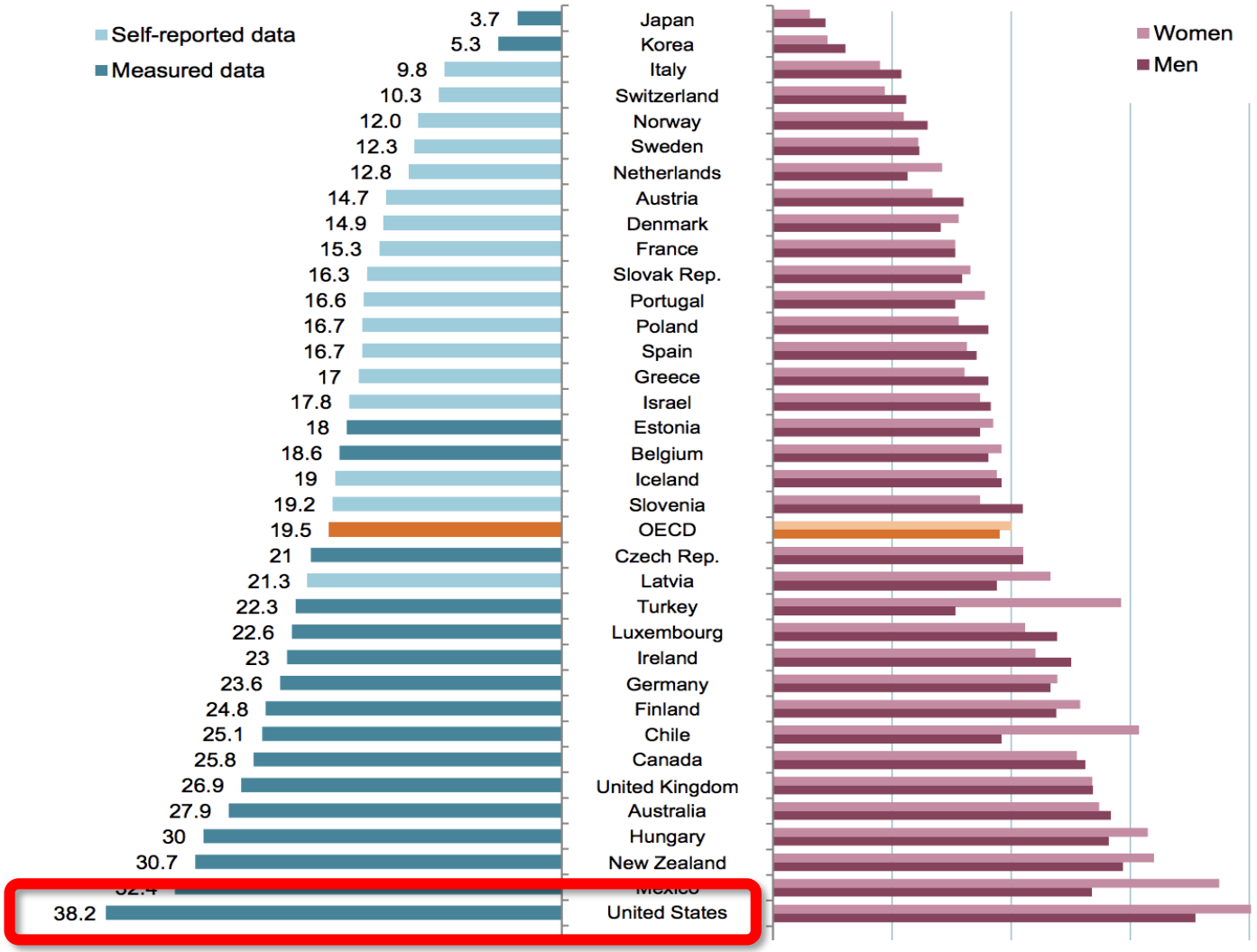
Obesity in America

1. *Obesity is a major cause of **morbidity** and **mortality***
2. *> **2.8 million** adults die globally from obesity-related diseases*
    a. *~ **400,000 preventable deaths annually** in America*
3. *Estimated **$210 billion** in healthcare costs annually (**21%**)*

Bueno, NB, et al. Br J Nutr (2013)

Cawley, J. J Health Econ (2012)

Figure 1: Obesity among adults, 2015 or nearest year



OECD. Obesity Updated (2017)

15% *of people maintain weight loss in the long term*

Bueno, NB, et al. Br J Nutr (2013)

Why is it so hard to lose weight?

The Metabolic Set Point

Body Weight Homeostasis

- ✓ ***Decrease*** *in basal metabolic rate*
- ✓ ***Increase*** *in exercise efficiency*
- ✓ ***Neuro-hormonal*** *regulation of satiety*

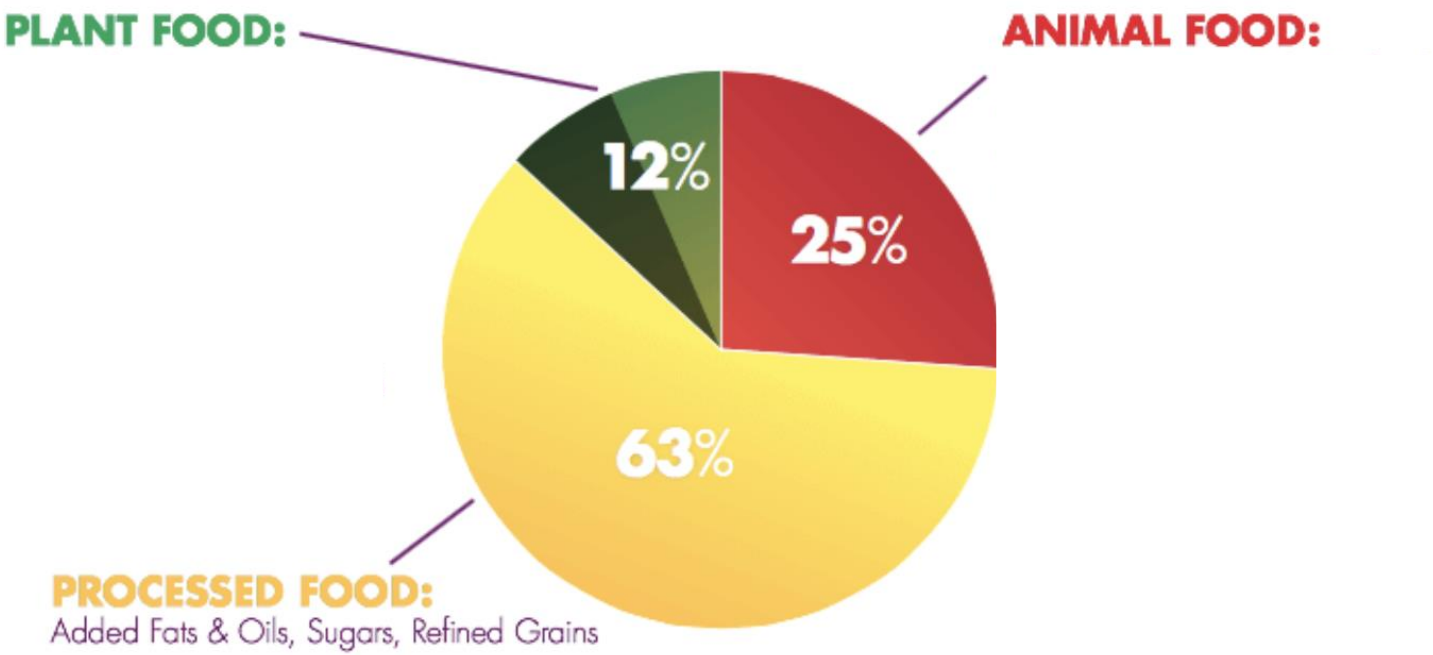
Greenway FL, Int J Obes (2015)

In addition,
there is no magic pill…

So, what do we recommend?

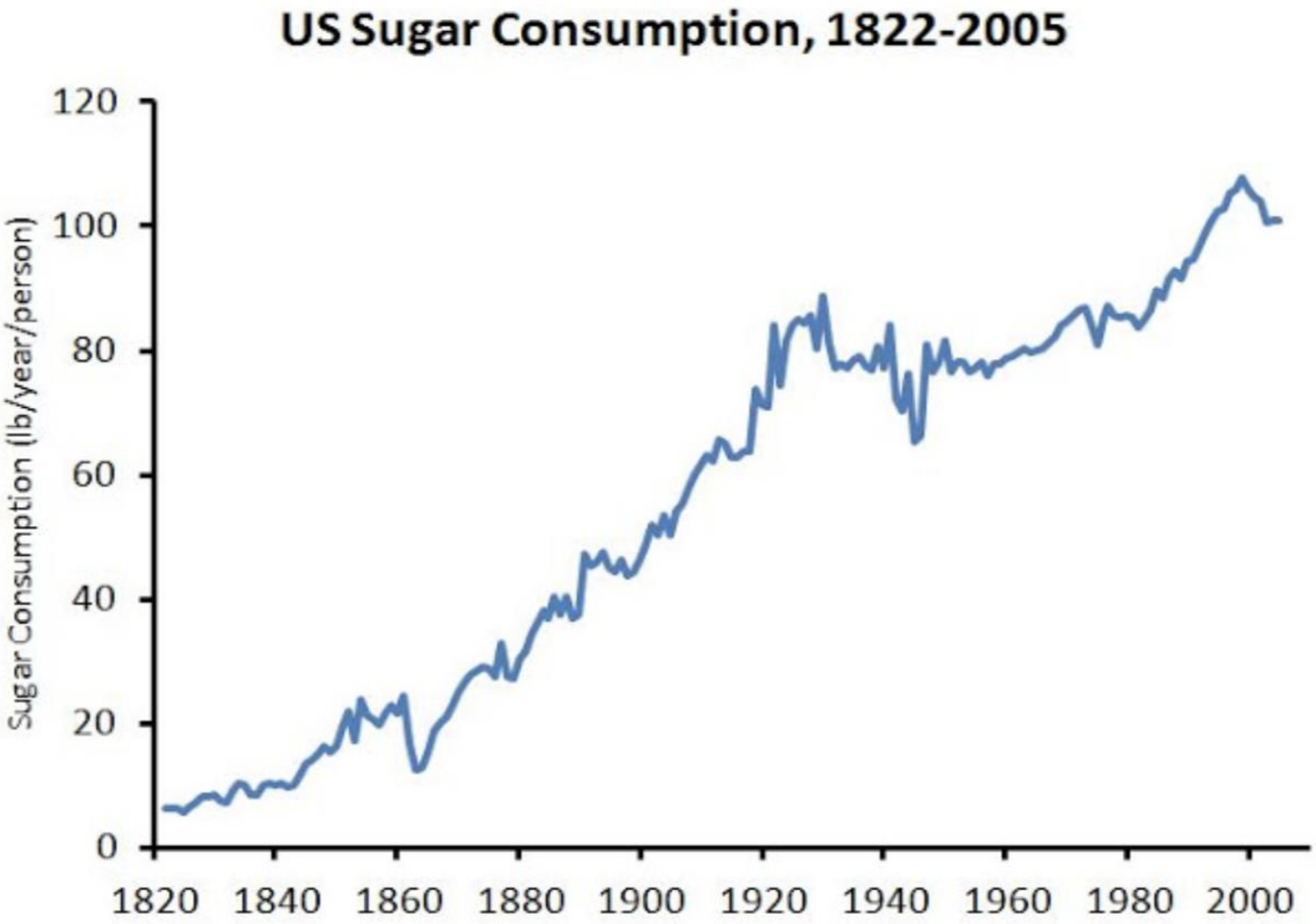
Healthy, Low Fat Diets

U.S. FOOD CONSUMPTION
AS A % OF CALORIES



Source: USDA Economic Research Service, 2009; www.ers.usda.gov/publications/EIB33; www.ers.usda.gov/Data/FoodConsumption/FoodGuideIndex.htm#calories
New York Coalition for Healthy School Food * www.healthyschoolfood.org
Special thanks to Joel Fuhrman, MD, author of ***Disease Proof Your Child: Feeding Kids Right*** * Graphics by MichelleBando.com

http://www.nyu.edu/sustainability/pdf/NYCHSF_FoodGraph2.pdf



http://www.businessinsider.com/chart-american-sugar-consumption-

Potential Problems with Low Fat Diets

1. *Americans consume a lot of processed food*
    a. ***High in Refined Sugar***
        i. ***High glycemic index***
        ii. ***Weight gain***
        iii. ***Metabolic syndrome***

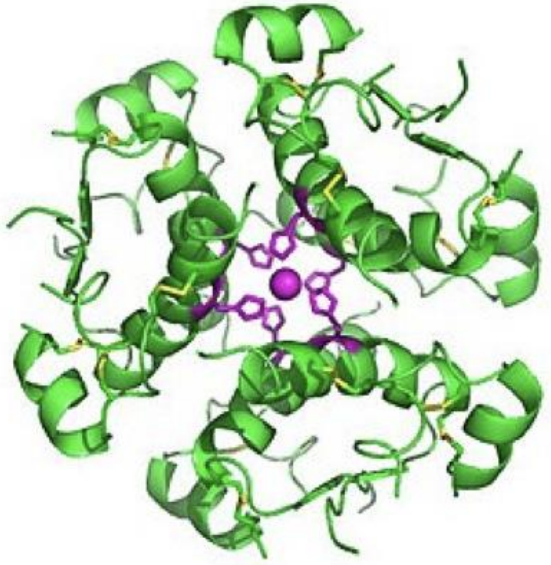
Paoli, A. Int J Environ Res Public Health (2014)

How does sugar cause weight gain?

Insulin and Glucagon:

Blood sugar regulation

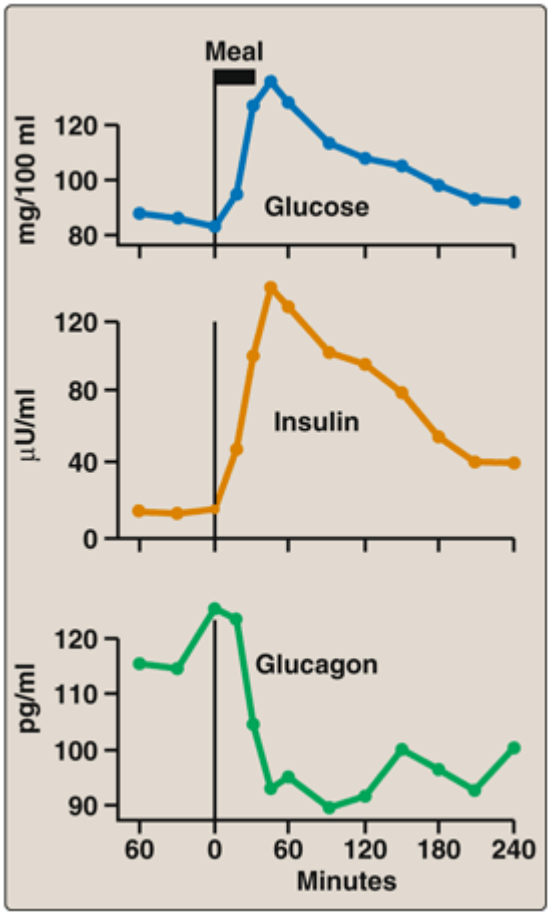
Insulin



1. *Shifts glucose into cells*
2. *Promotes weight gain and* ***anabolic metabolism***
3. *Suppresses glucagon and catabolism*

Stryer L, *Biochemistry* (1995)

Blood Sugar Regulation



To Summarize

1. *Large portion of our population trying to lose weight*
2. *American diet is very **high in refined carbohydrates***
3. *Foods with high glycemic index trigger **insulin release***
4. *Insulin release = **anabolism***
5. *Weight gain leads to **metabolic syndrome***

More importantly…

*I gained **50** pounds in residency…*

Reversing a 50 pound weight gain = ***Intense Clinical Relevance***

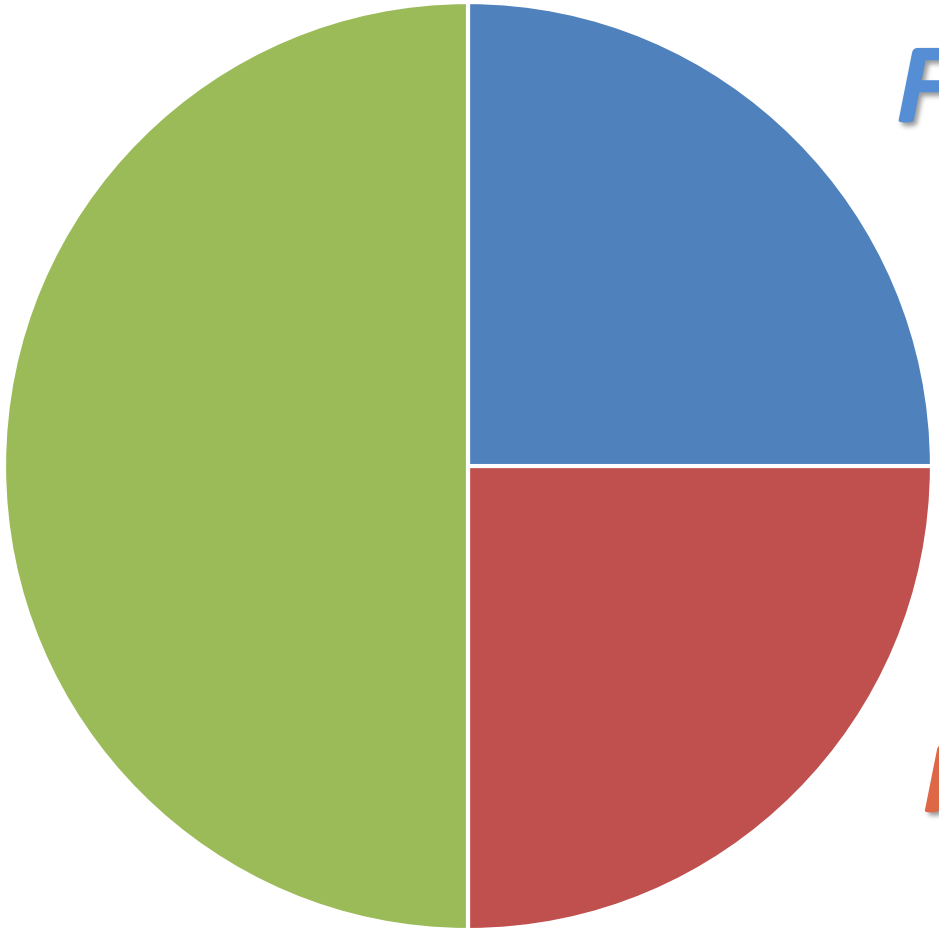
Can I use this knowledge to facilitate weight loss?

Objectives

1. ***Identify Clinical Relevance***
2. ***Define the Physiology of the Ketogenic Diet***
3. ***Explore Efficacy and Safety of the Ketogenic Diet***
4. ***Determine the Clinical Utility of the Ketogenic Diet***

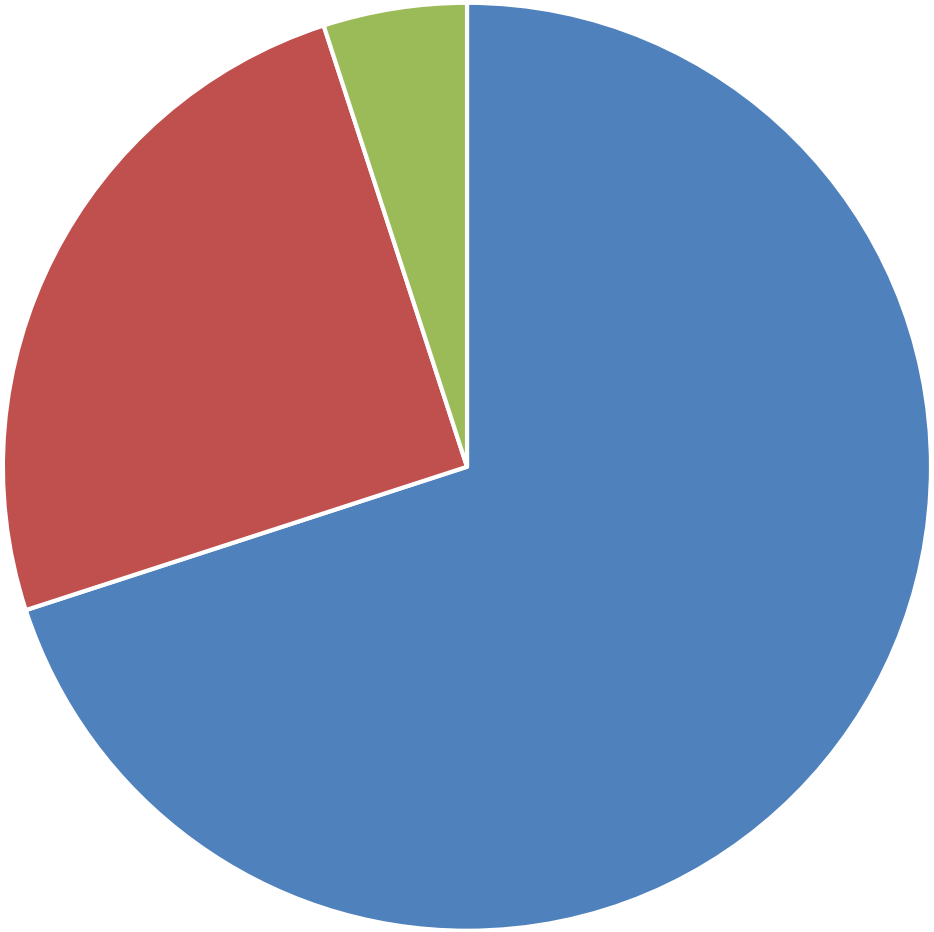
The Ketogenic Diet

1. ***Very low*** *carbohydrate diet*
    a. *Typically* ***< 20 g*** *of carbohydrates daily or*
    *<****10%*** *of total caloric intake from carbs*


FAT
Carbs
Protein

Carbohydrate
<20 g

Protein
1 g/kg



FAT

Why would this make you lose weight?

1. *Depletion of glycogen stores → diuresis*
2. *Glucagon release leads to fat metabolism*
3. *Oxidation of fatty acids in the liver and release of* ***ketones bodies***

Paoli A. Int J Environ Res Public Health (2014)

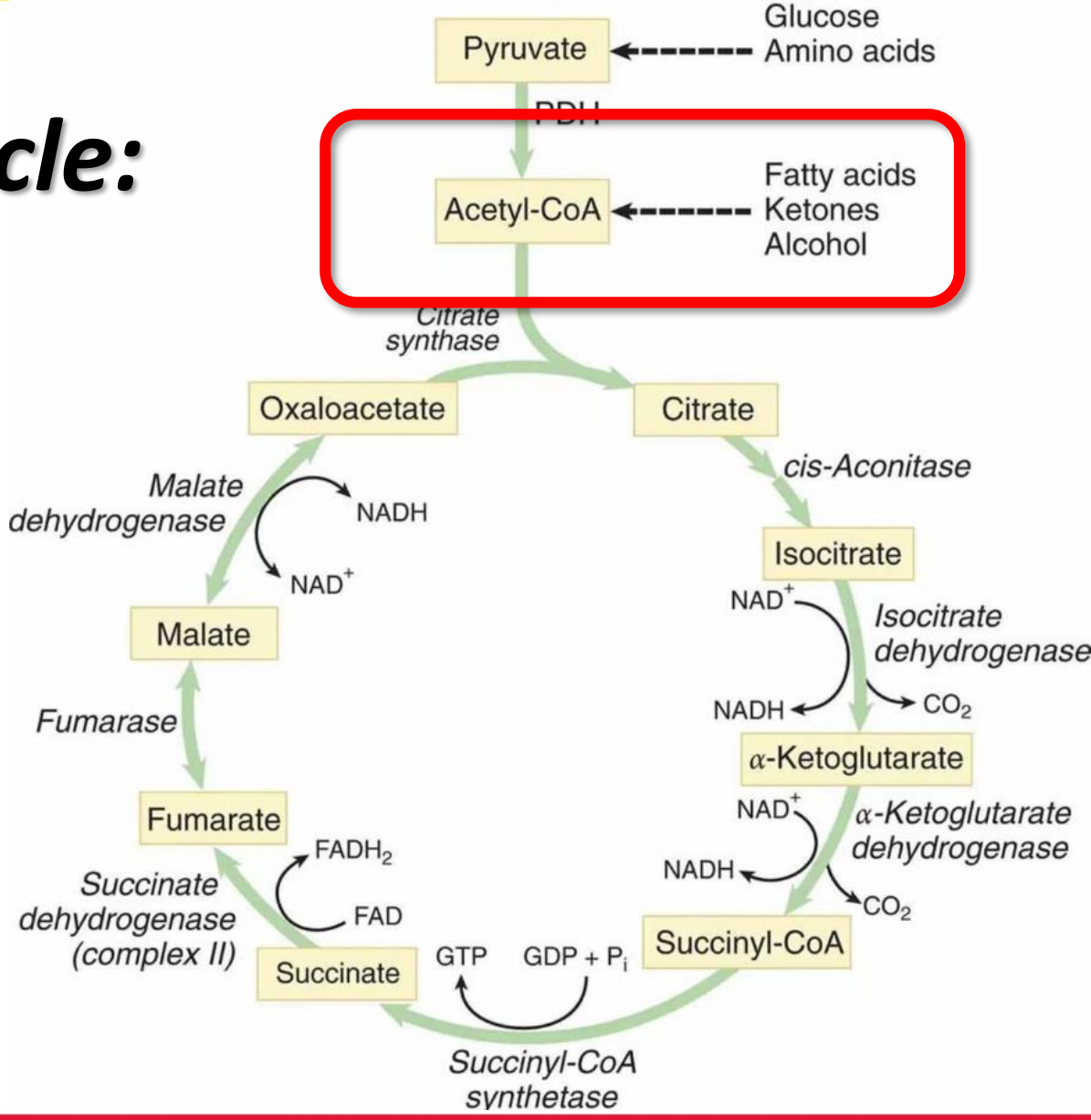
How are ketones utilized?

Beta-hydroxybutyrate → Acetoacetate →

Acetoacetyl-CoA → 2 molecules of ***Acetyl-CoA***

Paoli A. Int J Environ Res Public Health (2014)

The Krebs Cycle:



How is this different than DKA?

1. *Dietary ketosis is a **controlled process***
2. *Ketone concentration of **~ 8 mmol/L** (vs **30**)*
3. *Body **buffers** the ketones, pH remains **normal***

Manninen A. J Int Soc Sports Nutr (2004)

Putting it all together…

1. *Low carb diets lead to **depletion of glycogen***
2. *A conversion to **fat metabolism** occurs*
3. *Ketone bodies are an **effective** energy source*
4. *Clinically **different** entity than DKA*

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Is the ketogenic diet effective for weight loss?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 17, 2008 VOL. 359 NO. 3

Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet

Iris Shai, R.D., Ph.D., Dan Schwarzfuchs, M.D., Yaakov Henkin, M.D., Danit R. Shahar, R.D., Ph.D., Shula Witkow, R.D., M.P.H., Ilana Greenberg, R.D., M.P.H., Rachel Golan, R.D., M.P.H., Drora Fraser, Ph.D., Arkady Bolotin, Ph.D., Hilel Vardi, M.Sc., Osnat Tangi-Rozental, B.A., Rachel Zuk-Ramot, R.N., Benjamin Sarusi, M.Sc., Dov Brickner, M.D., Ziva Schwartz, M.D., Einat Sheiner, M.D., Rachel Marko, M.Sc., Esther Katorza, M.Sc., Joachim Thiery, M.D., Georg Martin Fiedler, M.D., Matthias Blüher, M.D., Michael Stumvoll, M.D., and Meir J. Stampfer, M.D., Dr.P.H., for the Dietary Intervention Randomized Controlled Trial (DIRECT) Group

DIRECT Trial

Dietary Intervention Randomized Control Trial

Design

1. Randomized 322 individuals by diet

a. Mean age of 52

b. Mean BMI of 31

Shai I. et al. NEJM (2004)

Design

2. 3 Study Groups

a. *Low carb diet → **Atkins***

b. *Mediterranean diet*

c. *Traditional low fat diet (based on AHA guidelines)*

3. Primary end point was weight loss

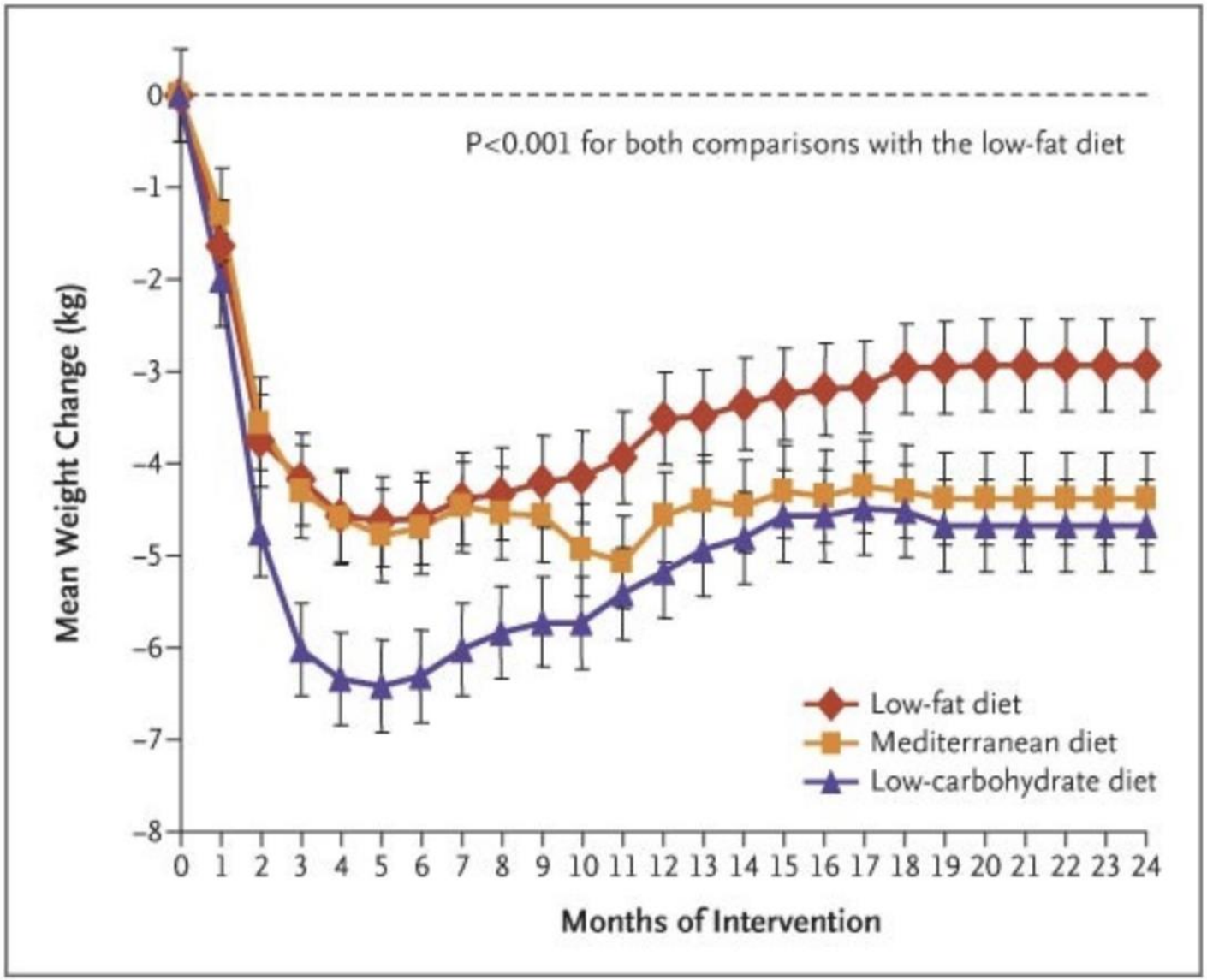
Shai I. et al. NEJM (2004)

Notes

1. ***Low carb diet was not calorie restricted***
    a. *<20 g carbs daily*
2. ***Low fat and Mediterranean diets were calorie limited***
    a. *1500 for women, 1800 for men*
3. ***Subjects were predominantly male (86%)***

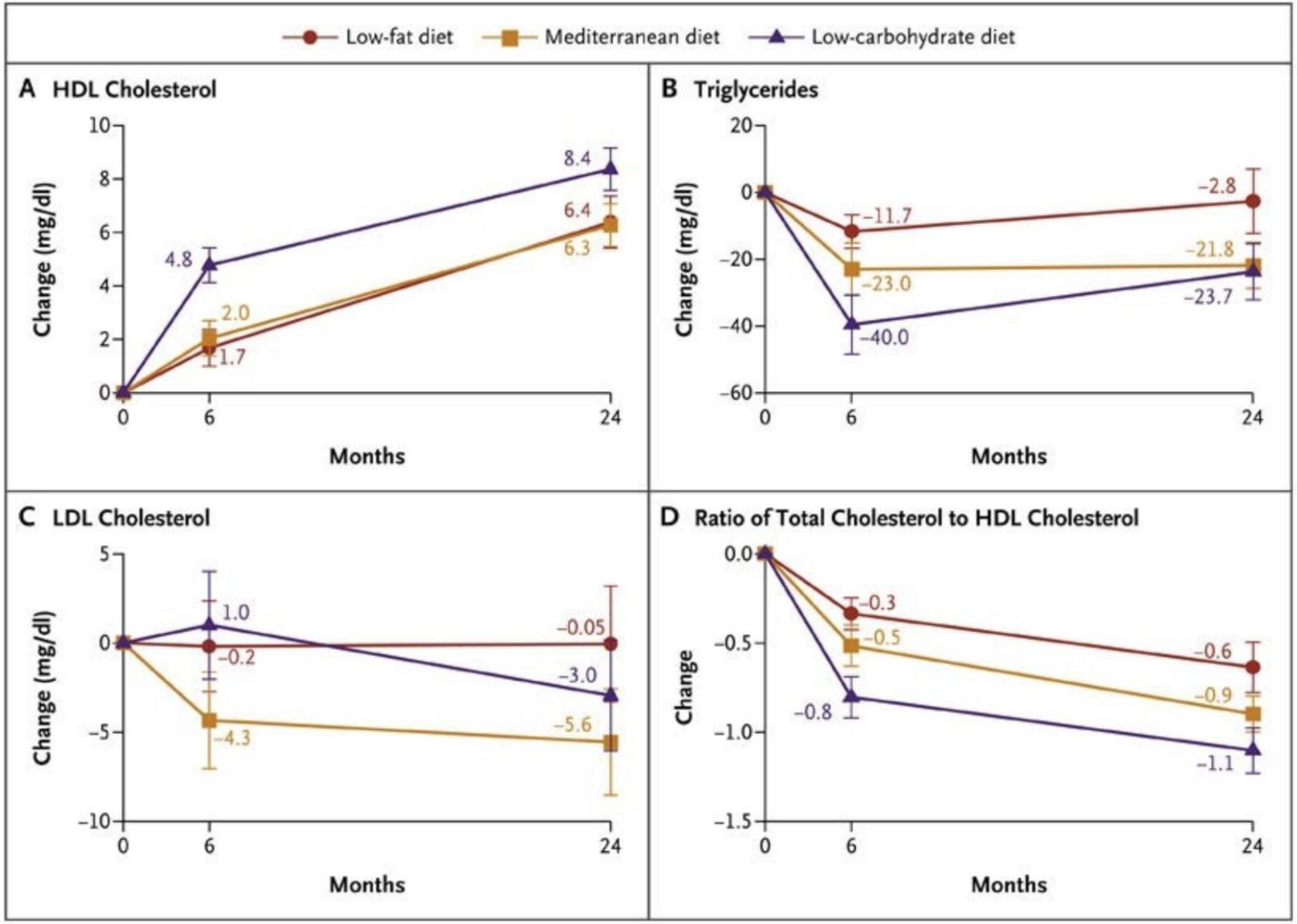
Shai I. et al. NEJM (2004)

Figure 2



Shai I. et al. NEJM (2004)

Figure 3



Shai I. et al. NEJM (2004)

Conclusions

*Low carb diets are **as safe** as low fat diets*

*and **more effective** for weight loss.*

Schwartzfuchs D. NEJM (2012)

4 Years Later

1. *Serum CVD biomarkers remained **favorable***

2. Weight loss remained **significant**

Schwartzfuchs D. NEJM (2012)

Have these results been replicated in women?

JAMA The Journal of the American Medical Association

Comparison of the Atkins, Zone, Ornish, and LEARN Diets for Change in Weight and Related Risk Factors Among Overweight Premenopausal Women

The A TO Z Weight Loss Study: A Randomized Trial

Christopher D. Gardner, PhD
Alexandre Kiazand, MD
Sofiya Alhassan, PhD
Soowon Kim, PhD
Randall S. Stafford, MD, PhD
Raymond R. Balise, PhD
Helena C. Kraemer, PhD
Abby C. King, PhD

Context Popular diets, particularly those low in carbohydrates, have challenged current recommendations advising a low-fat, high-carbohydrate diet for weight loss. Potential benefits and risks have not been tested adequately.

Objective To compare 4 weight-loss diets representing a spectrum of low to high carbohydrate intake for effects on weight loss and related metabolic variables.

Design, Setting, and Participants Twelve-month randomized trial conducted in the United States from February 2003 to October 2005 among 311 free-living, overweight/obese (body mass index, 27-40) nondiabetic, premenopausal women.

Intervention Participants were randomly assigned to follow the Atkins (n=77), Zone (n=79), LEARN (n=79), or Ornish (n=76) diets and received weekly instruction for 2 months, then an additional 10-month follow-up.

Main Outcome Measures Weight loss at 12 months was the primary outcome. Secondary outcomes included lipid profile (low-density lipoprotein, high-density lipoprotein, and non–high-density lipoprotein cholesterol, and triglyceride levels), percentage of body fat, waist-hip ratio, fasting insulin and glucose levels, and blood pressure. Outcomes were assessed at months 0, 2, 6, and 12. The Tukey studentized range

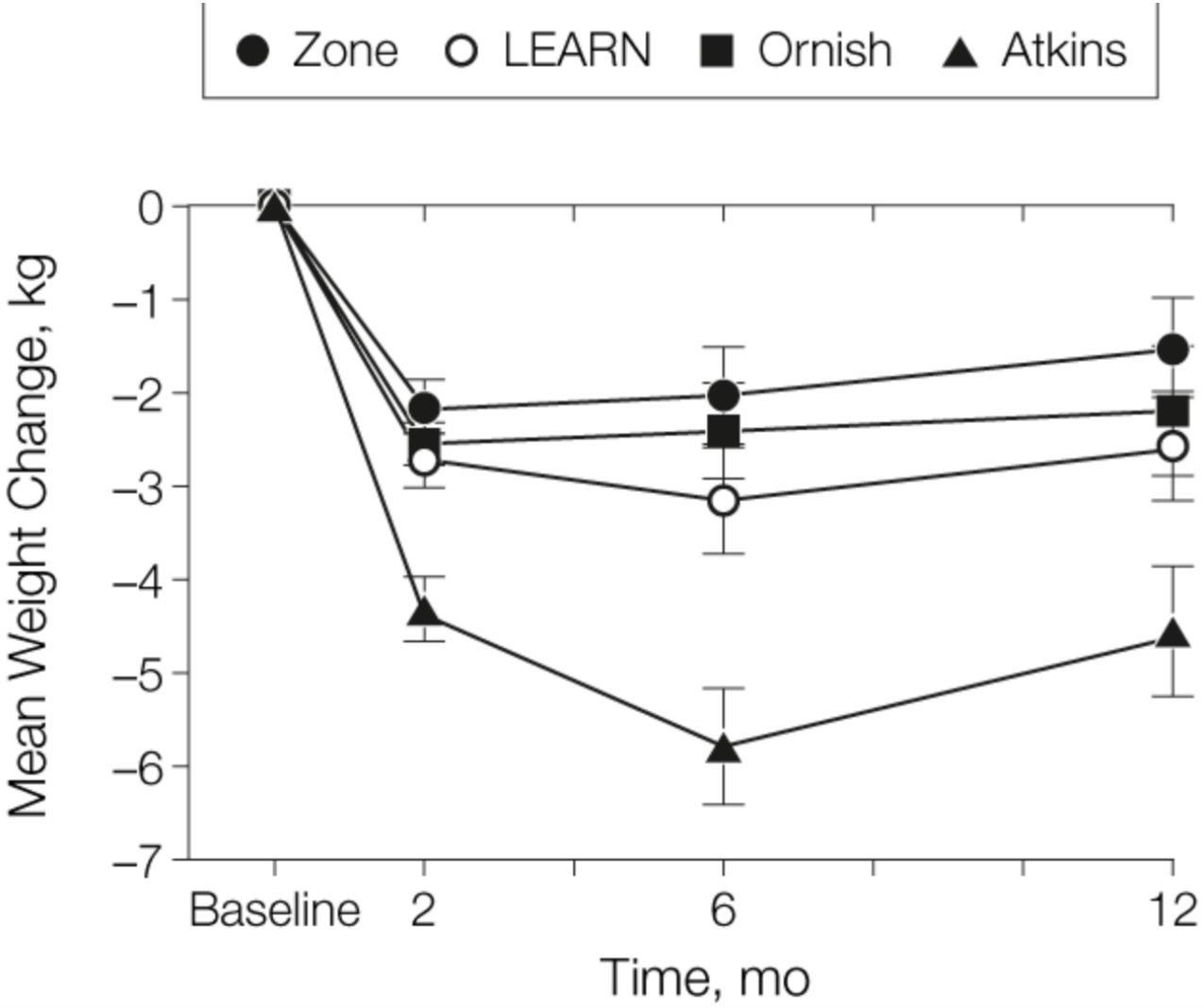
THE ONGOING OBESITY EPIdemic,[1] along with its health costs and consequences[2] and the health benefits of weight loss,[3-6] have been well established. National dietary weight loss guidelines (ie,

The A TO Z Weight Loss Study

1. *Randomized **311** women to diet*
   a. *Mean age **40***
   b. *Mean BMI **> 30***
2. *Primary endpoint was **weight loss** at 1 year*

Gardner et al. JAMA (2007)

Figure 2



Gardner et al. JAMA (2007)

Secondary Outcomes

1. *No adverse effect of Atkins on lipid variables*
2. *Atkins had greatest reduction in triglycerides (P = 0.01)*
3. *Atkins had greatest reduction in BP (P = <0.01)*
4. *Atkins had greatest reduction in BMI (P = 0.01)*

Gardner et al. JAMA (2007)

Conclusions

1. *The ketogenic diet is also **efficacious** for weight loss in a large population of women*

2. *CVD risk modification **as encouraging** as DIRECT Trial*

Gardner et al. JAMA (2007)

How does ketogenic diet affect lean muscle mass?

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Body Composition Changes After Very-Low-Calorie Ketogenic Diet in Obesity Evaluated by 3 Standardized Methods FREE

Diego Gomez-Arbelaez, Diego Bellido, Ana I. Castro, Lucia Ordoñez-Mayan, Jose Carreira, Cristobal Galban, Miguel A. Martinez-Olmos, Ana B. Crujeiras, Ignacio Sajoux, Felipe F. Casanueva Author Notes

The Journal of Clinical Endocrinology & Metabolism, Volume 102, Issue 2, 1 February 2017, Pages 488–498, https://doi.org/10.1210/jc.2016-2385

Published: 18 October 2016 **Article history** ▾

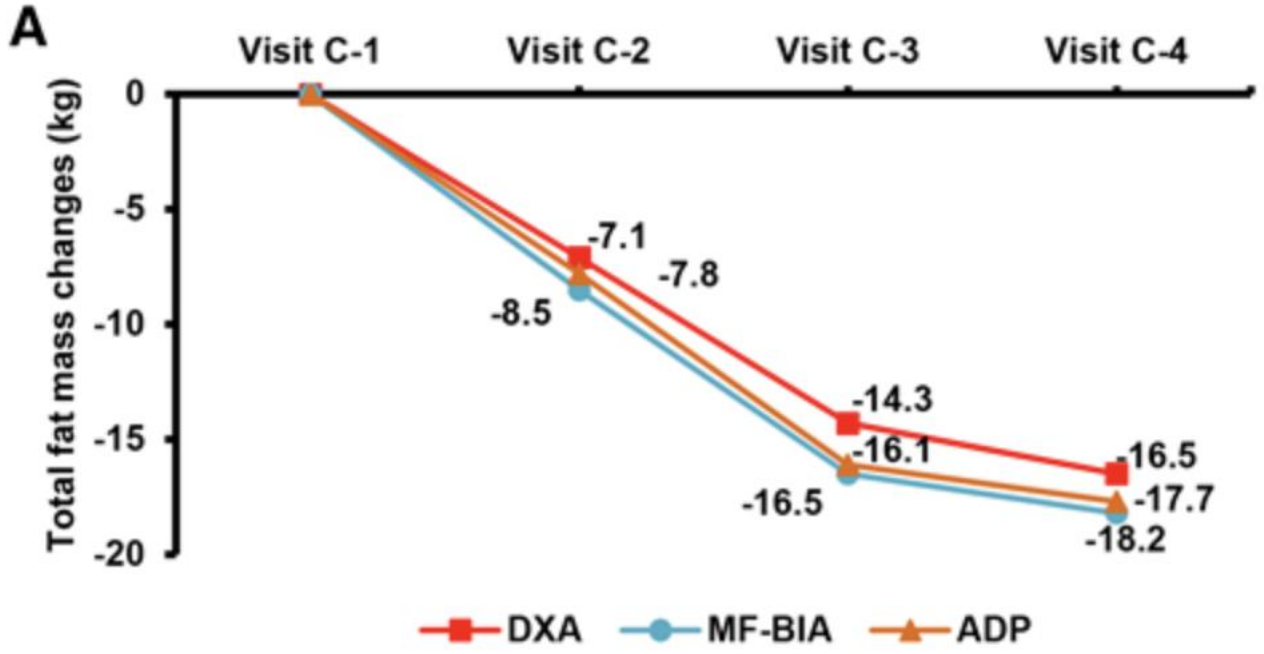
Design

1. ***20 patients***
    a. *Given **800 calories** per day*
    b. *< **50 g** carbs daily*
    c. *All achieved a **20 kg** weight loss*
2. ***Ketosis confirmed by capillary blood***
3. ***Body composition evaluated by 3 validated tools***

Gomez-Arbelaez D. J Clin Endocrinol Metab (2017)

Change in Fat Mass

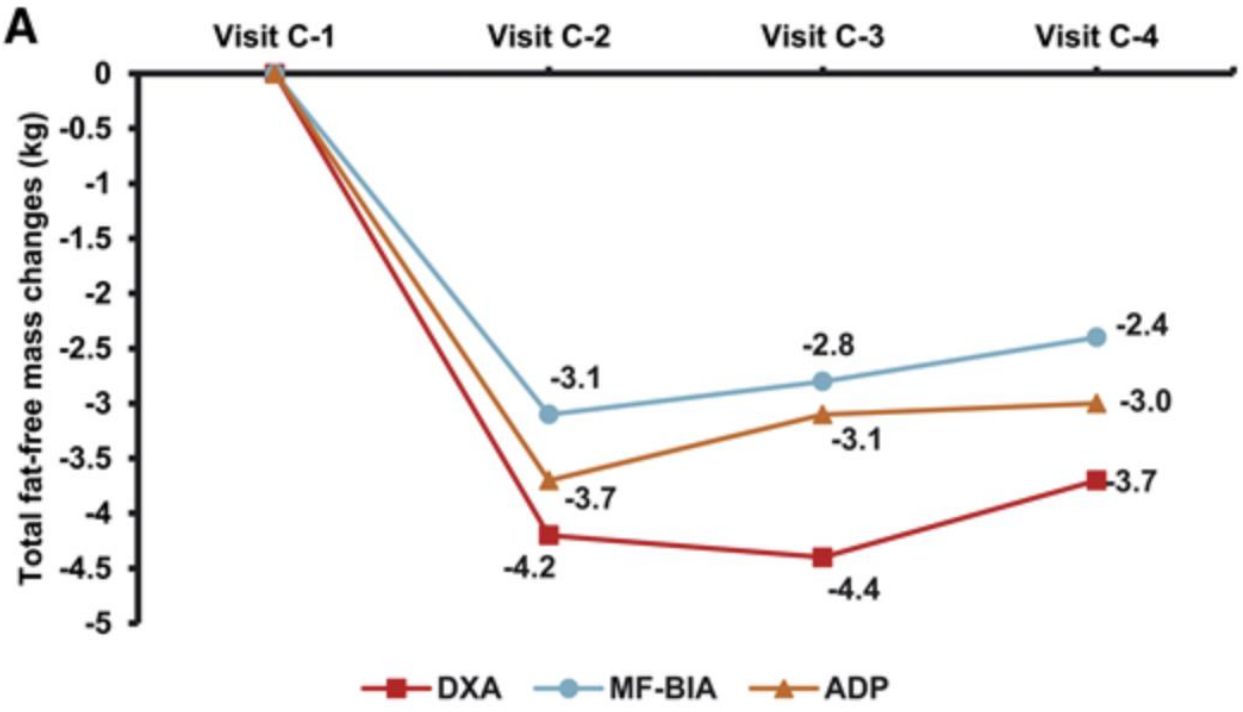
Figure 2.



Gomez-Arbelaez D. J Clin Endocrinol Metab (2017)

Change in Lean Mass

Figure 3.



Gomez-Arbelaez D. J Clin Endocrinol Metab (2017)

Conclusions

*Low carb diets cause weight loss predominantly from **visceral fat** and preserve lean muscle*

Gomez-Arbelaez D. J Clin Endocrinol Metab (2017)

How could anyone comply with this diet?

Study participants who are in ketosis spontaneously restrict caloric intake…

European Journal of Clinical Nutrition (2013) **67**, 759–764

www.nature.com/ejcn

ORIGINAL ARTICLE

Ketosis and appetite-mediating nutrients and hormones after weight loss

P Sumithran[1], LA Prendergast[1,2], E Delbridge[1], K Purcell[1], A Shulkes[3], A Kriketos[1] and J Proietto[1]

BACKGROUND/OBJECTIVES: Diet-induced weight loss is accompanied by compensatory changes, which increase appetite and encourage weight regain. There is some evidence that ketogenic diets suppress appetite. The objective is to examine the effect of ketosis on a number of circulating factors involved in appetite regulation, following diet-induced weight loss.
SUBJECTS/METHODS: Of 50 non-diabetic overweight or obese subjects who began the study, 39 completed an 8-week ketogenic very-low-energy diet (VLED), followed by 2 weeks of reintroduction of foods. Following weight loss, circulating concentrations of glucose, insulin, non-esterified fatty acids (NEFA), β-hydroxybutyrate (BHB), leptin, gastrointestinal hormones and subjective ratings of appetite were compared when subjects were ketotic, and after refeeding.
RESULTS: During the ketogenic VLED, subjects lost 13% of initial weight and fasting BHB increased from (mean ± s.e.m.) 0.07 ± 0.00 to 0.48 ± 0.07 mmol/l ($P<0.001$). BHB fell to 0.19 ± 0.03 mmol/l after 2 weeks of refeeding ($P<0.001$ compared with week 8). When participants were ketotic, the weight loss induced increase in ghrelin was suppressed. Glucose and NEFA were higher, and amylin, leptin and subjective ratings of appetite were lower at week 8 than after refeeding.
CONCLUSIONS: The circulating concentrations of several hormones and nutrients which influence appetite were altered after weight loss induced by a ketogenic diet, compared with after refeeding. The increase in circulating ghrelin and subjective appetite which accompany dietary weight reduction were mitigated when weight-reduced participants were ketotic.

European Journal of Clinical Nutrition (2013) **67,** 759–764; doi:10.1038/ejcn.2013.90; published online 1 May 2013

Keywords: appetite; ketosis; very-low-energy diet; weight loss

Findings

1. *Ghrelin levels were **lower** than expected*
2. *Ketotic patients **did not feel hungry***
3. *Ketosis seemingly **suppresses appetite***

Sumithran P. Eur J Clin Nutr (2013)

What about the metabolic set point?

Does keto promote weight regain?

JAMA Network™

PRELIMINARY COMMUNICATION

Effects of Dietary Composition on Energy Expenditure During Weight-Loss Maintenance

Cara B. Ebbeling, PhD
Janis F. Swain, MS, RD
Henry A. Feldman, PhD
William W. Wong, PhD
David L. Hachey, PhD
Erica Garcia-Lago, BA
David S. Ludwig, MD, PhD

Context Reduced energy expenditure following weight loss is thought to contribute to weight gain. However, the effect of dietary composition on energy expenditure during weight-loss maintenance has not been studied.

Objective To examine the effects of 3 diets differing widely in macronutrient composition and glycemic load on energy expenditure following weight loss.

Design, Setting, and Participants A controlled 3-way crossover design involving 21 overweight and obese young adults conducted at Children's Hospital Boston and Brigham and Women's Hospital, Boston, Massachusetts, between June 16, 2006, and June 21, 2010, with recruitment by newspaper advertisements and postings.

Intervention After achieving 10% to 15% weight loss while consuming a run-in diet, participants consumed an isocaloric low-fat diet (60% of energy from carbohydrate, 20% from fat, 20% from protein; high glycemic load), low–glycemic index diet (40% from carbohydrate, 40% from fat, and 20% from protein; moderate glycemic

MANY PEOPLE CAN LOSE weight for a few months, but most have difficulty maintaining clinically

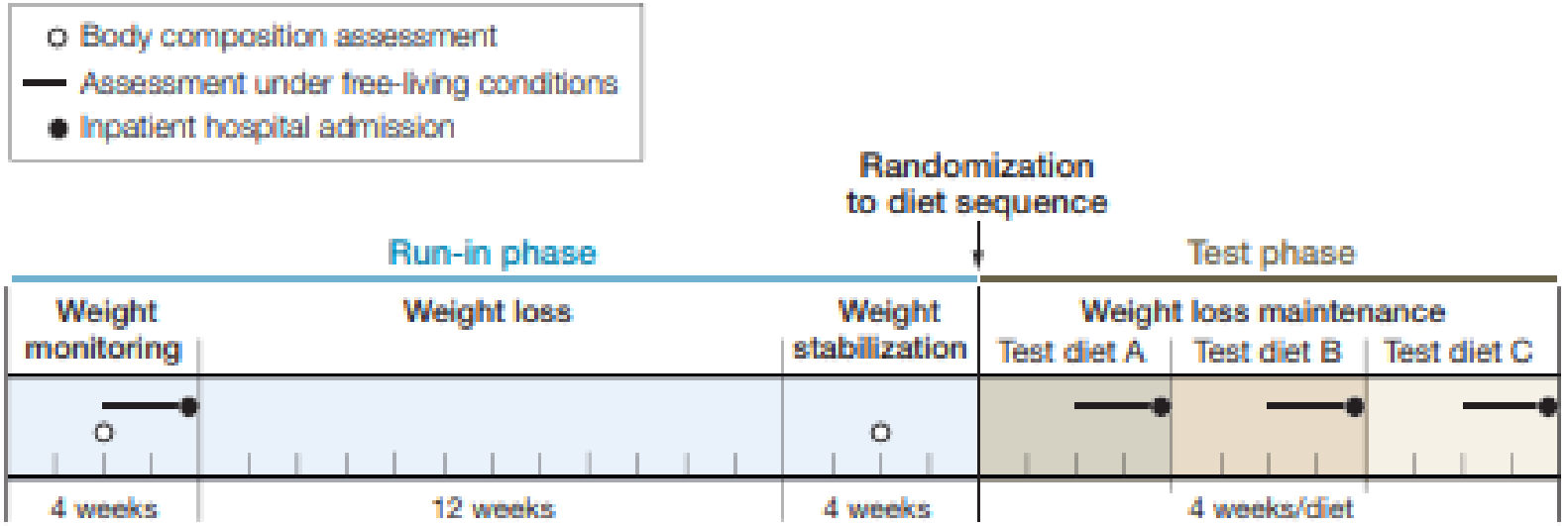
Design

1. *Enrolled 21 obese adults*
2. *Achieved a **10 - 15 %** weight reduction*
3. *Trialed **3** maintenance diets*
4. *Monitored basal and total **energy expenditure***

Ebbeling CB. JAMA Network (2012)

Design

Figure 1. Study Design of the Run-in and Test Phases



Ebbeling CB. JAMA Network (2012)

Results

1. ***Decrease in energy expenditure greatest for the low-fat diet***

    a. *REE: -205 [-265 to -144] kcal/day*

    b. *TEE: -403 [-606 to -239] kcal/day*

2. ***Decrease in energy was the least for the very low carbohydrate diet***

    1. *REE: -138 [-198 to -77] kcal/day*

    2. *TEE: -97 [-281 to 86] kcal/day*

Ebbeling CB. JAMA Network (2012)

In Summary…

1. *Ketogenic diet is **effective** for weight loss*
2. *CVD risk factors **appear to improve** with ketogenic diet*
3. *Rapid loss does not negatively impact **lean body mass***
4. *Metabolism may be **preserved** on a very low carb diet*
5. *Ketosis modifies **appetite and satiety***

What about safety?

Objectives

1. ***Identify Clinical Relevance***
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Why not find out for myself?

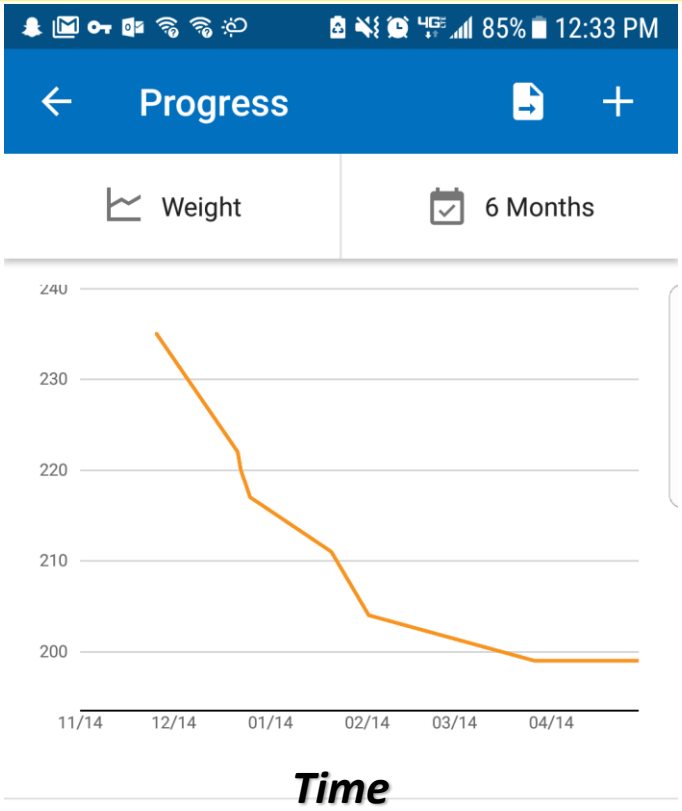
My Plan

- ✓ *Buy a food scale*
- ✓ *Track my macronutrients*
- ✓ *Eat < 20 grams of carbs daily*
- ✓ *Monitor urine ketones*
- ✓ *Maintain an exercise plan*

My Stats

- ✓ Starting weight of 236 lbs
- ✓ Averaged 1200 calories per day
- ✓ Averaged 100 gram of protein daily
- ✓ Averaged 22 grams of carbs daily

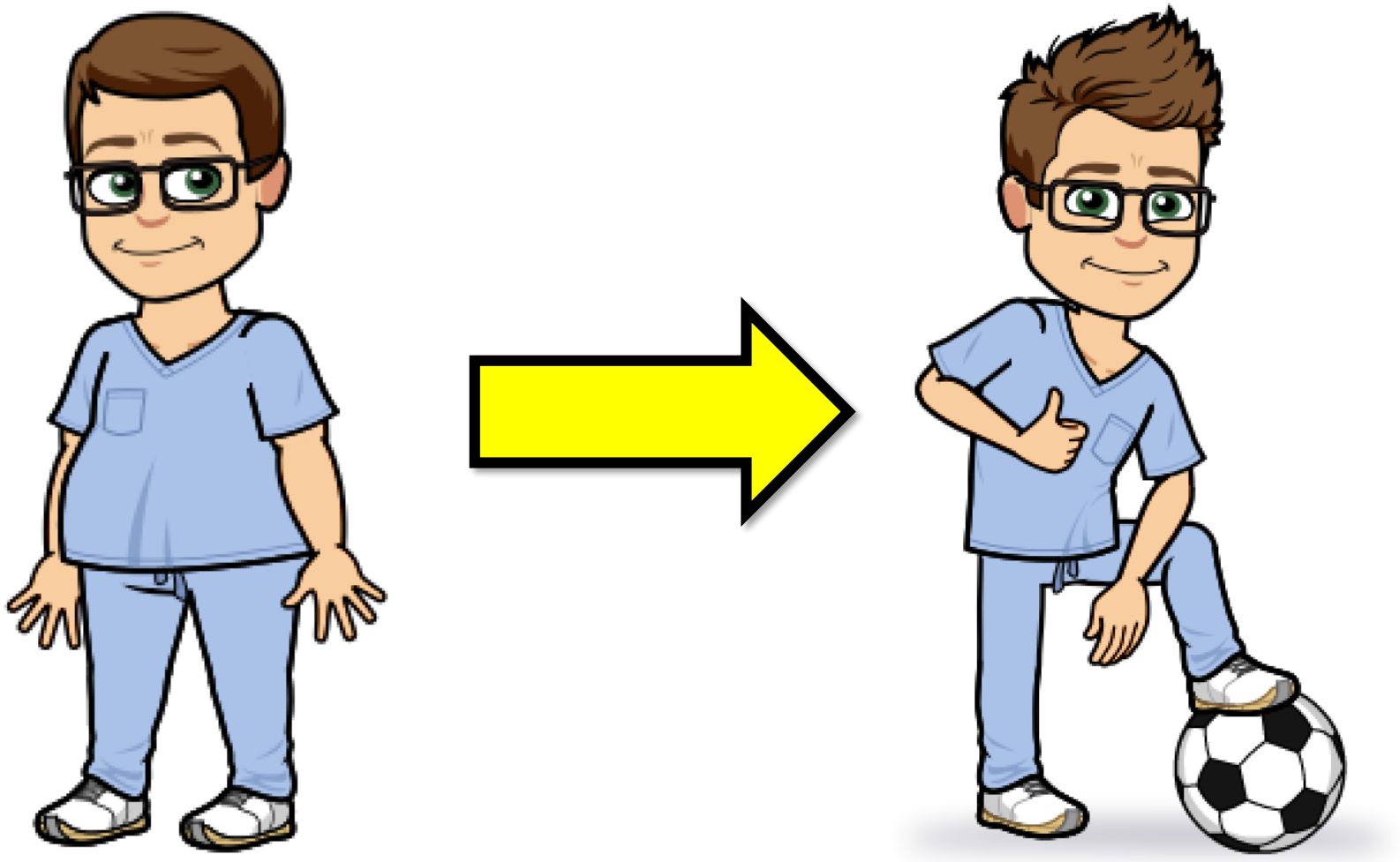
Weight (lbs.)



Time

At the end of the day…

- ✓ *I lost **38 pounds** in 15 weeks*
- ✓ *Roughly **0.4 pounds** per day*
- ✓ *Decreased blood pressure by **10 mmHg***
- ✓ *Decreased waist size by **6 inches***



Conclusions

- ✓ *The ketogenic can be safe and effective*
- ✓ *It offers certain advantages over traditional diets*
- ✓ *Keto may appeal to certain patients*
- ✓ *Likely an effective tool for rapid and potentially durable weight loss*

1. Bueno, Nassib Bezerra, et al. “Very-Low-Carbohydrate Ketogenic Diet v. Low-Fat Diet for Long-Term Weight Loss: a Meta-Analysis of Randomised Controlled Trials.” *British Journal of Nutrition*, vol. 110, no. 07, July 2013, pp. 1178–1187., doi:10.1017/s0007114513000548.
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14. Ebbeling CB. Effects of Dietary Composition on Energy Expenditure During Weight-Loss Maintenance. JAMA Internal Medicine. https://jamanetwork.com/journals/jama/fullarticle/1199154. Published June 27, 2012. Accessed May 29, 2018.