

# Ketosis and the Ketogenic Diet:

## A Deep Dive

**Scott Bergman, DC**

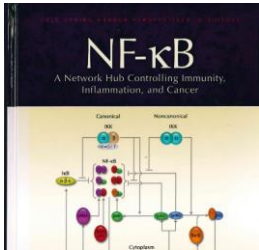
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# Objectives

- Understand the factors driving body weight regulation—from metabolism to the intestinal microbiome
- Discuss the clinical management of patients who are overweight
- Review the role of macronutrient modification in weight management with a focus on low carbohydrate approaches
- Discuss integration of targeted probiotics and nutritional supplements to support healthy weight loss and weight maintenance efforts
- Discuss the clinical implications of ketogenic diets, from peripheral metabolism to brain health
- Explore supporting factors for ketogenic lifestyle
  - Nutritional supplement support (e.g. medium-chain triglycerides [MCT], beta-hydroxybutyrate [ $\beta$ HB])

# NF-κB is at the center of the inflammatory process



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)  
ScienceDirect  
Elsevier  
Ageing Research Reviews 7 (2008) 83–105  
Review  
Activation of innate immunity system during aging:  
NF-κB signaling is the molecular culprit of inflamm-aging  
Antoni Salminen<sup>a,b,\*</sup>, Paul M. Henson<sup>a</sup>, Johannes Grub<sup>c</sup>, Amy Kimmelman<sup>d</sup>

“Our conclusion is that NF-κB signaling seems to be the culprit of inflamm-aging, since this signaling system integrates the intracellular regulation of immune responses in both aging and age-related diseases.”

- Virtually every chronic disease has inflammation as an underlying mechanism
- Modulation of NF-κB is the key strategy addressing any chronic disease

1. Introduction  
A number of innovative  
...  
\*Corresponding author. E-mail: [antoni.salminen@utu.fi](mailto:antoni.salminen@utu.fi) (A. Salminen).

“Activation of the NF-κB/Rel transcription family, by nuclear translocation of cytoplasmic complexes, plays a central role in inflammation through its ability to induce transcription of proinflammatory genes.”

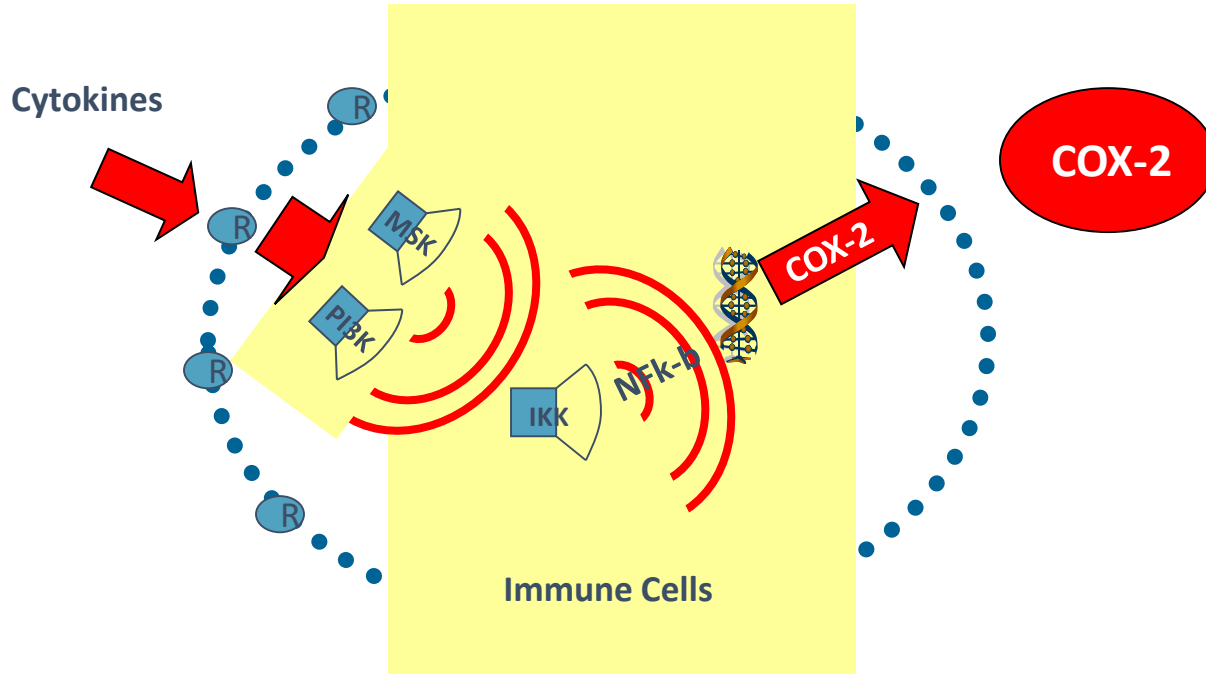
The expression of NF-κB protein can provide...  
The transcription of NF-κB protein can provide...  
The transcription of NF-κB protein can provide...  
The transcription of NF-κB protein can provide...

Salminen *et al* Ageing Res Rev 2008; 7:83-105  
Tak *et al*. J Clin Invest 2001 107(1):7-11



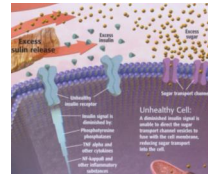
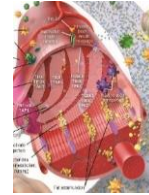
# Kinase signaling activates NFk-b creating COX-2

Kinases translate signals from cytokines to turn on the genes that create COX-2

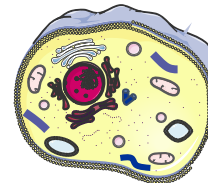
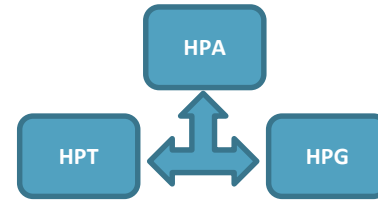


# Inflammation » Nu.R.D. » Obesity » Disease

- A pro-inflammatory Standard American Diet is the primary contributor to inflammation
- Physical, chemical and emotional stress increase inflammation
  - Deplete nutrients
  - Increase the need for nutrients
- Nutrient Reserve Depletion
  - Increases stress in the organ
  - Lowers immune defenses
- 68,000 ICD-10 codes can be associated with inflammation and at least one Nu.R.D.

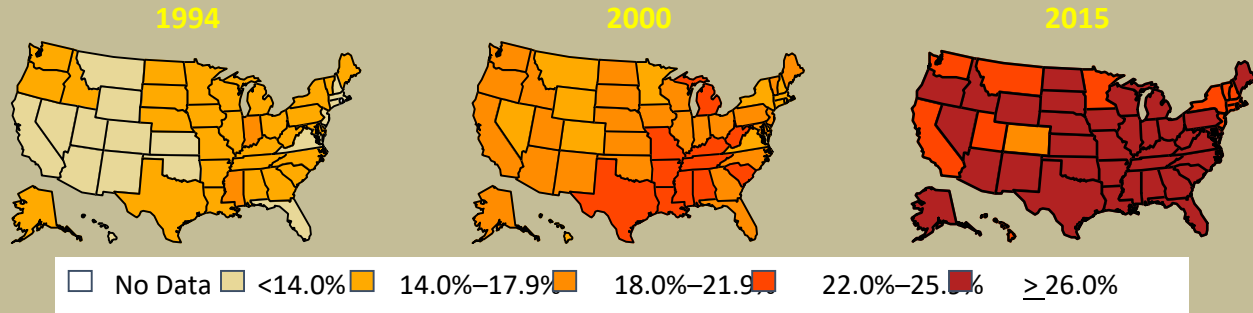


Credit: Lancaster University

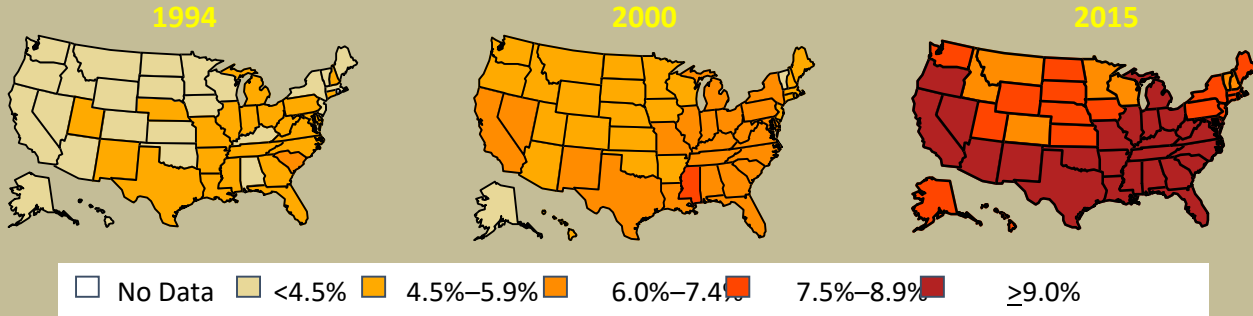


# Age-adjusted prevalence of obesity and diagnosed diabetes among US adults

## Obesity (BMI $\geq 30$ kg/m<sup>2</sup>)



## Diabetes



CDC's Division of Diabetes Translation. United States Surveillance System available at <http://www.cdc.gov/diabetes/data>



# Understanding the basics

- Obesity imposes devastating health and financial tolls on individuals and society
- Clinicians are at the forefront of the obesity epidemic, often with limited time and resources
- In order for clinicians to tackle the obesity epidemic, we need evidenced-based treatments that are practical, affordable and feasible to implement in real world settings



# Obesity can be defined in many ways— including as a disorder of fat mass

With excess energy being stored as fat

## Body energy reserves (1000kcal)

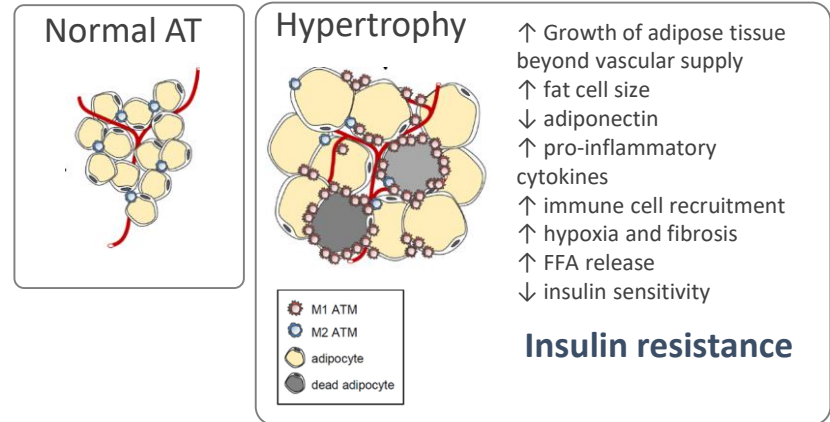
	Thin	Normal	Obese
Carbohydrate	2	2	2
Protein	25	30	35
Fat	30-60	100	200

Volek et al., *European Journal of Sport Science*, 2015;15(1):13–20

# Obesity could also be a dysfunction within adipose tissue....

## Adipose tissue remodeling in obesity

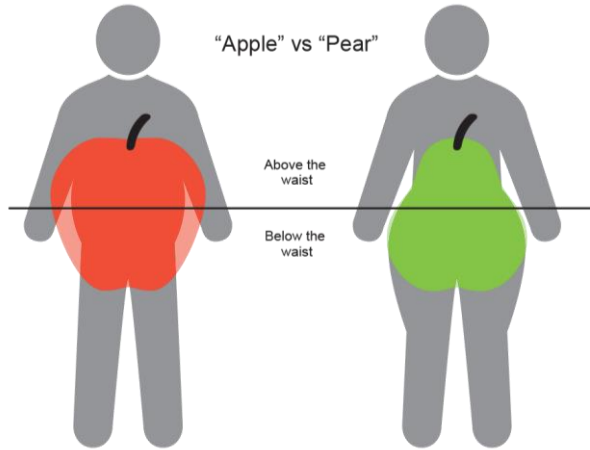
- Changes in the size of the adipocytes affect the microenvironment of expanded fat tissues.
- Concurrently, stromal vascular cells in the adipose tissue, including immune cells, are involved in numerous adaptive processes, such as dead adipocyte clearance, adipogenesis, and angiogenesis.
- Uncontrolled inflammatory responses, leading to systemic low-grade inflammation and metabolic disorders, such as insulin resistance.



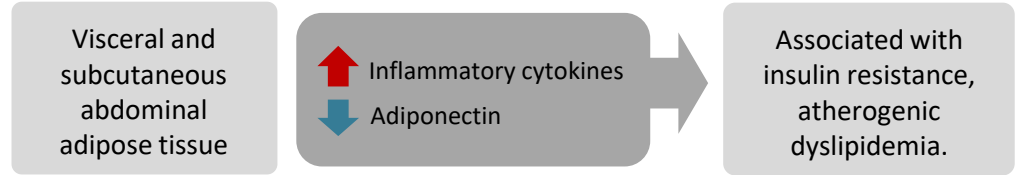
**Note:** cross-talk between adipose and other organs—adiposopathy most often results in metabolic disease when accompanied by:

- Dysfunction of other body organs
- Limitations of the metabolic “flexibility” of other body organs to mitigate the pathogenic metabolic, endocrine, and immune responses promoted by obesity

# Obesity has distinct adipose tissue deposition patterns



- Adipose tissue is an endocrine organ. Different depots have different metabolic activity<sup>1</sup>

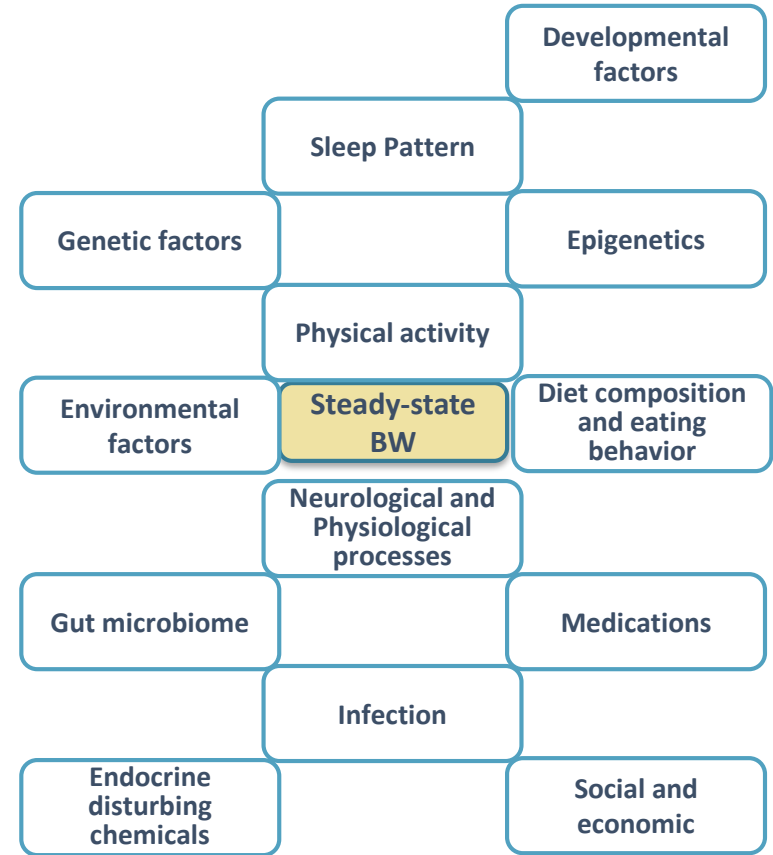


- Waist circumference is a surrogate measure of abdominal and visceral fat
  - 54.2% of US population have elevated waist circumference
  - 43.5% of men, and 64.7% of women<sup>2</sup>
  - In women, this figure is rising to a greater degree than expected by BMI increase<sup>3</sup>

1. Bays. *Curr Opin Endocrinol Diabetes Obes* 2014; 21:345–351  
2. Ford et al. *JAMA* 2014; 312(11):1151-3  
3. Freedman & Ford. *Am J Clin Nutr* 2015;101(3):425-31

# There are numerous potential contributors to its pathogenesis

- The etiology of obesity is believed to be multifactorial
- Alterations in any of these factors will result in changes to this steady-state BW → cause obesity
- To identify effective treatments, we need to establish obesity's underlying causes



TOS, 2015

Schwartz et al., *Endocrine Reviews*, 2017;38:1-30

OMA, 2015

BW = body weight

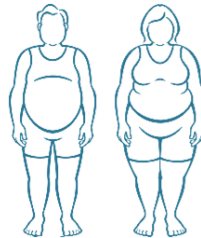


# Adverse consequences of increased body fat are numerous and often linked to comorbid conditions

- The adverse health consequences of increased body fat are more than simply “co-morbidities” or “associated risk factors”
- Multiple pathogenic adipocyte and/or adipose tissue endocrine and immune dysfunctions contribute to metabolic disease
- Multiple pathogenic physical forces from excessive body fat cause damage to other body tissues

## Some specific and systemic issues found with obesity

- Cardiovascular issues including stroke and MI
- Respiratory issues including asthma
- Musculoskeletal issues including OA, back pain, myalgias
- Gastrointestinal issues including reflux, hernias, gall stones
- Psychological issues including depression, self-esteem
- Metabolic issues including MetS, prediabetes and T2D
- Gender specific issues:
  - Women (hyperandrogenism, hirsutism, acne, PCOS, menstrual disorders, infertility, preeclampsia and gestational diabetes)
  - Men (hypoandrogenism, hyperestrogenemia, erectile dysfunction, low sperm count, infertility)



# Losing weight reduces morbidity and mortality risks along with lowered healthcare costs

Obesity complication	Weight loss required for therapeutic benefit (%)
Diabetes (prevention)	3-10
Hypertension	5 to >15
Dyslipidemia	3 to >15
Hyperglycemia (elevated HbA1c)	3 to >15
NAFLD	10
Sleep apnea	10
Osteoarthritis	5-10
Stress incontinence	5-10
Gastroesophageal reflux disease	5-10 in women; 10 in men
Polycystic ovary syndrome	5-15 (>10 optimal)

- Weight loss of 10-15% BW among adults with overweight and obesity could lead to gross Medicare savings of \$6,456- \$13,474 per person over ten years.<sup>2</sup>
- Enrolling overweight and obese adults age 60–64 with prediabetes in a weight loss program could save Medicare \$1.8–\$2.3 billion over the following ten years.<sup>3</sup>

1. Cefalu et al. *Diabetes care*. 2015;38(8):1567-1582.

2. Thorpe et al. *Health Econ Rev*. 2013; 3: 7.

3. Thorpe KE, and Yang Z. *Health Aff*. 2011;30(9):1673-9.

# Improving outcomes begins by correctly identifying the patient who is overweight/obese

## Common methods of measurement used in determining obesity

- **Body mass index (BMI)** is a simple index that is commonly used to classify overweight and obesity in adults by using weight and height. However easy to routinely track but not ideal as sole measure (poor sensitivity). Different for different races and ethnicities. May not track with adiposity.
  - BMI  $\geq 25$  kg/m<sup>2</sup> for overweight
  - BMI  $\geq 30$  kg/m<sup>2</sup> for obesity.
- **Measurements of percent body fat**
  - Women  $\geq 32\%$  Men  $\geq 25\%$  (essential fat women 10-13% and men 2-5%). Body composition changes relevant to overall health and improvement in function.
- **Waist circumference (WC)**
  - Men  $\geq 40''$  (102cm) and women  $\geq 35''$  (88cm) (note differences in Asian men  $\geq 90$ cm and women  $\geq 80$ cm). Most relevant in providing additional information regarding adipose tissue deposition and metabolic dysfunction in those with BMI  $<35$ .

1. Evans EM, et al. *Int J Obes*. 2006 May;30(5):837-43.
2. Romero-Corral, et al, *Int J Obes*. 2008; 32(6):959-66
3. Misra, et al, *Int J Obes*. 2006 Jan;30(1):106-11.

# High carbohydrate intake and its impact on human health

- Diets with high-starch, low-fiber ratio are associated with a **higher risk of type 2 diabetes**<sup>1</sup>
- High carbohydrate intakes ( $\geq 74$  En%) may increase the risk for **metabolic syndrome**, while moderate fat intakes ( $\geq 20$  En%) may reduce the risk for metabolic syndrome in women<sup>2</sup>
- Dietary carbohydrate intake, glycemic index and glycemic load are positively associated with risk of **gastric cancer in male and Asian subgroups**<sup>3</sup>
- Sedentary lifestyle and high-carbohydrate intake are associated with **low-grade chronic inflammation and increased cardiovascular disease risk in post-menopausal women**<sup>4</sup>
- Higher blood glucose levels are associated with an **increased risk of dementia**<sup>5</sup>



1. AlEsa HB et al. *American Journal of Clinical Nutrition* 2015;102(6):1543-53

2. Park S et al. *International Journal of Food Sciences and Nutrition* 2017;68(4):479-487

3. Ye Y et al. *European Journal of Nutrition* 2017; 56(3):1169-1177

4. Alves BC et al. *Revista Brasileira de Ginecologia e Obstetrícia* 2016; 38(7):317-24

5. Crane PK et al. *The New England Journal of Medicine* 2013; 369:540-548

# Benefits of low carbohydrate intake on human health

- In a study with type 2 diabetics, a low-carbohydrate ketogenic diet led to **greater improvements in glycemic control**, and more frequent **medication reduction/elimination** than the low glycemic index diet<sup>1</sup>
- In a study of highly trained ultra-endurance athletes, a long-term, low carbohydrate ketogenic diet resulted in **high rates of fat oxidation**<sup>2</sup>
- The low-carbohydrate ketogenic diet has also been shown to induce **significant weight loss and improve fatty liver disease**<sup>3</sup>
- Low-carbohydrate diet is associated with **better vigilance attention and reduced self-reported confusion**<sup>4</sup>
- In a preclinical study, a low carbohydrate diet **slowed cancer development and progression**<sup>5</sup>



1. Westman EC et al. *Nutrition & Metabolism* 2008; 19(5):36

2. Volek JS et al. *Metabolism* 2016; 65(3):100-10

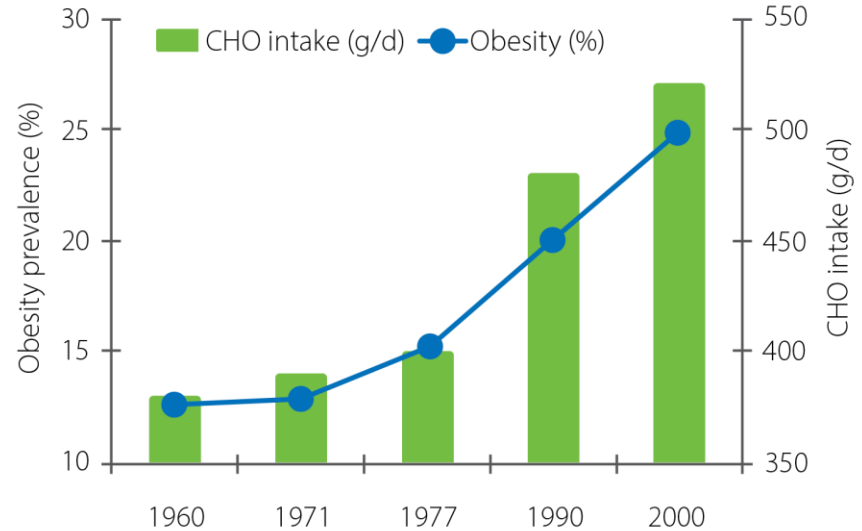
3. Tendler D et al. *Digestive Diseases and Sciences* 2007; 52(2):589-93

4. D'Anci KE et al. *Appetite* 2009; 52(1):96-103

5. Ho WV et al. *Cancer Research* 2011; 71(13): 4484-93

# Carbohydrate intake and obesity prevalence over time in the US between 1960 and 1997

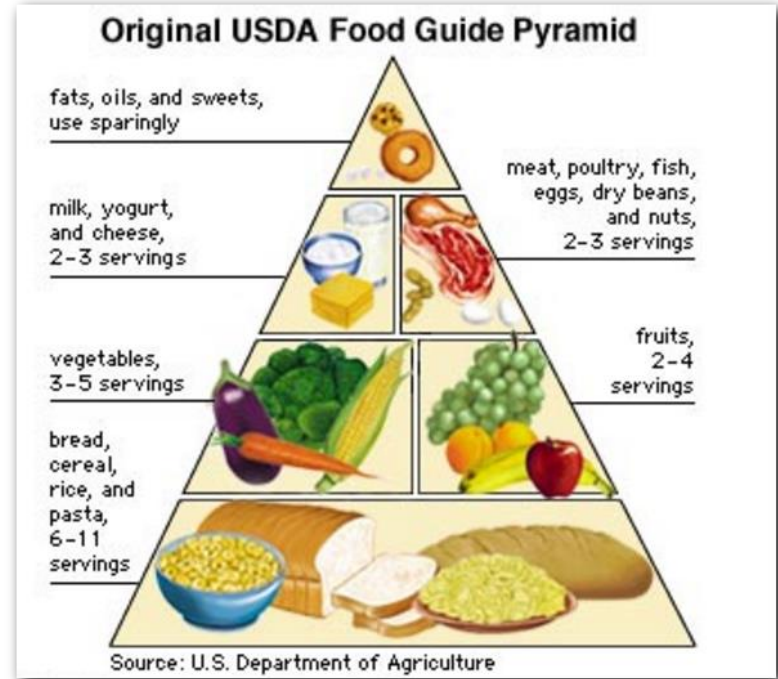
Prevalence of obesity and diabetes increased proportionately to the increase in consumption of refined carbohydrates in the US



Adapted from: Lee S Gross et al., *The American Journal of Clinical Nutrition*, 2004, 79:5, 774-9

# Lipid-hypothesis, fat phobias and fat facts

- Who decided saturated fat was bad?
- How did we determine processed carbs were healthy
- Why did we think PUFA's, from processed oils would reduce or prevent heart disease?



# Scientist who led the campaign against dietary fat

- The **K-ration** was an individual daily combat food ration for short term field operations
- Criticism of the K-ration
  - Was not fully evaluated and field tested
  - 3,200 Kcal but soldiers did not feel it provided enough energy



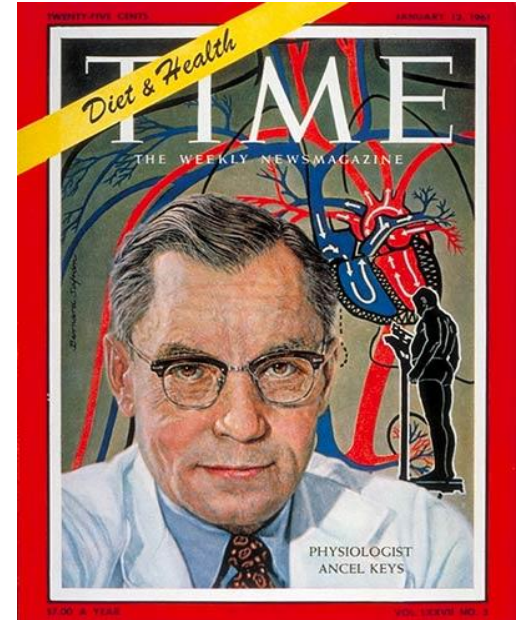
US Army, Signal Corps -

[http://www.qmmuseum.lee.army.mil/subsistence/KRation\\_Dinner.JPG](http://www.qmmuseum.lee.army.mil/subsistence/KRation_Dinner.JPG)



# Scientist who led the design of the K-Ration?

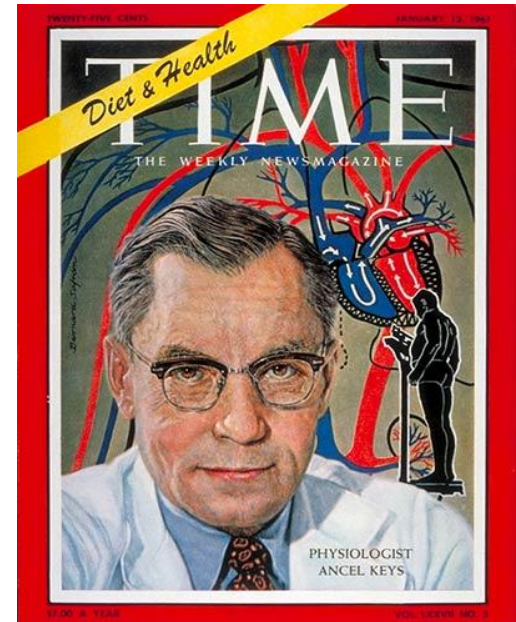
- Dr. Ancel Keys
  - Development of K-rations
  - Starvation Study
  - Seven Countries Study
    - (+) Note - Advocated the Mediterranean Diet
  - BMI best indicator of obesity
  - The Sugar Controversy



January 13, 1961 issue of [Time magazine](https://en.wikipedia.org/wiki/Time_magazine)  
Wikipedia: [https://en.wikipedia.org/wiki/Ancel\\_Keys](https://en.wikipedia.org/wiki/Ancel_Keys)

# Minnesota Starvation Study (1944)

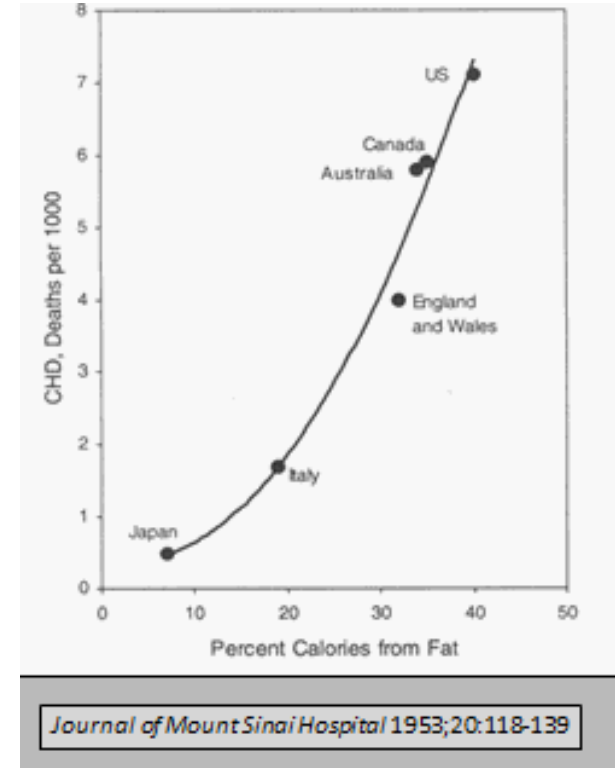
- 36 conscientious objectors
  - Objectors were being placed in virtual concentration camps
  - Studied the physical and mental effects of starvation on “volunteers”
  - A metabolic baseline for three months
    - 3,200 KCal
  - Semi Starvation Set for six months
    - 1,560 KCal per day potatoes, rutabagas, turnips, bread and macaroni
  - Studied the physical and mental effects of different refeeding protocols for three months.
- Study confirmed that prolonged semi-starvation produces depression, hysteria and hypochondriasis, preoccupation with food, reduced libido, social withdrawal and isolation
- Reported decline in concentration, comprehension and judgment capabilities



January 13, 1961 issue of [Time magazine](https://en.wikipedia.org/wiki/Time_magazine)  
Wikipedia: [https://en.wikipedia.org/wiki/Ancel\\_Keys](https://en.wikipedia.org/wiki/Ancel_Keys)

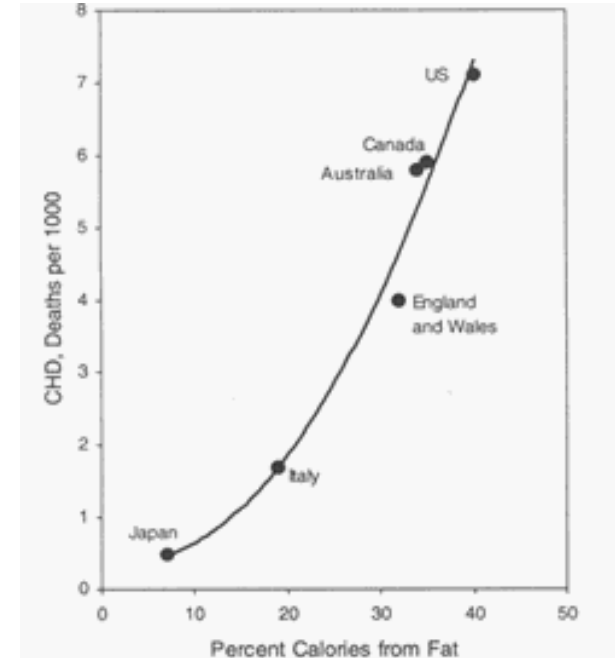
# Seven Countries Study

- Keys presented his Diet-Lipid-Heart Disease hypothesis to the WHO in 1955
  - Saturated fat increases cholesterol
  - Cholesterol causes heart disease
  - Mediterranean-style diet low in animal fat protected against heart disease
- American Heart Association appeared on television and endorsed the hypothesis
- This resulted in the American government recommending that people adopt a low-fat diet in order to prevent heart disease



# Possible flaws in the study?

- A massive epidemiological study
  - Used to find correlation
  - Experimentation confirms causation
- The original study involved 22 countries, the data from the other countries were omitted for undisclosed reasons

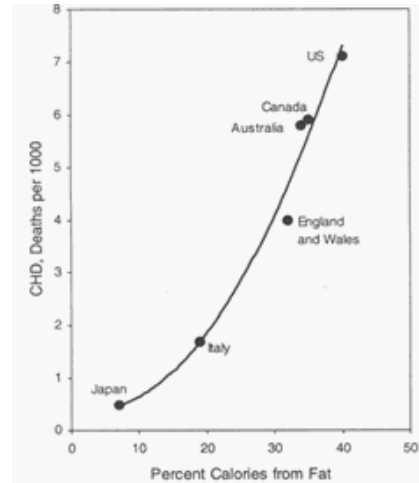


*Journal of Mount Sinai Hospital* 1953;20:118-139

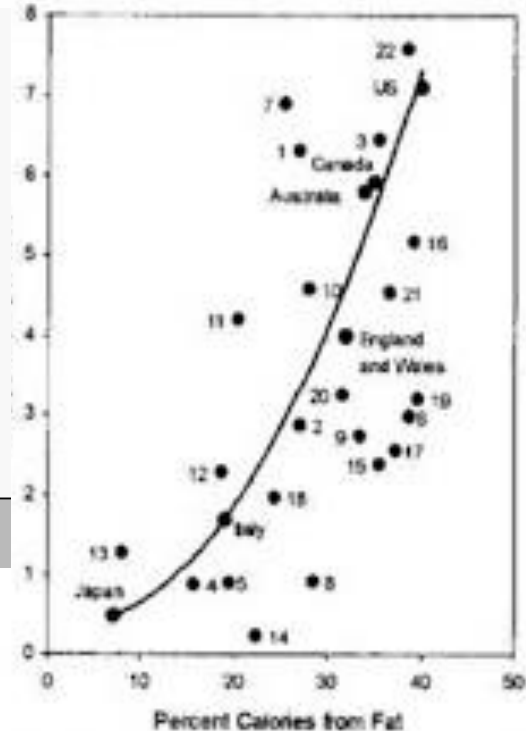
# Possible flaws in the study?

“When the data from all 22 countries were analyzed, no correlation between fat and heart disease was found.”

(Yerushalmy and Hilleboe 1957)

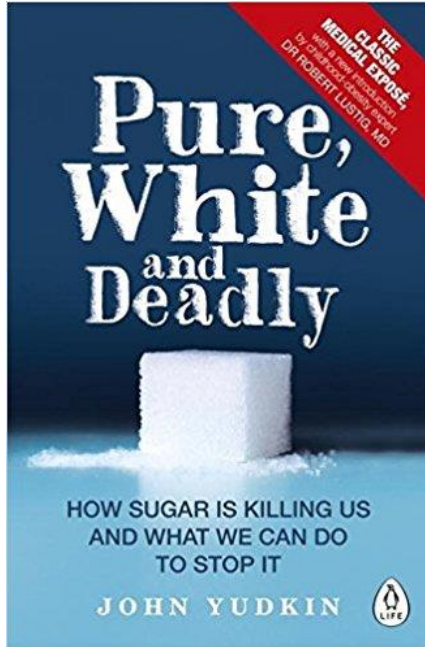


*Journal of Mount Sinai Hospital* 1953;20:118-139



1. Australia
2. Italy
3. Canada
4. Ceylon
5. Chile
6. Denmark
7. Finland
8. France
9. W. Germany
10. Ireland
11. Israel
12. Italy
13. Japan
14. Mexico
15. Holland
16. New Zealand
17. Norway
18. Portugal
19. Sweden
20. Switzerland
21. Great Britain
22. USA

# The sugar controversy



- Johnathan Yudkin
  - Yudkin analyzed trends in diet, and trends in coronary mortality, in the UK between 1928 and 1954
  - Found no evidence that total fat was the direct cause of coronary thrombosis
  - The closest relationship between coronary deaths and any single dietary factor was with sugar
- The final chapter lists several examples of Dr. Keys' attempts to interfere with the funding of his research and to prevent the publication of his book

# Framingham Heart Study (1948 to present)

**Test if serum cholesterol and the development of CHD are related to:**

- **The caloric balance:**
  - Findings opposite - More calories the men consumed, the lower were their serum cholesterol levels
- **Level of animal fat intake vs vegetable fat intake:**
  - Findings: No association between percent of calories from fat and serum cholesterol level was shown
- **Level of protein intake**
  - Findings: There was a trivial negative correlation between daily protein intake (in grams) and serum cholesterol level
- **Level of cholesterol intake**
  - Findings: There is no indication of a relationship between dietary cholesterol and serum cholesterol level

## The Sydney Diet Heart Study (1966-73)

Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from and updated meta-analysis.

*BMJ*. 2013;346:e8707.

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## Minnesota Coronary Experiment (1968-73)

Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment

*BMJ*. 2016;353:i1246.

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## MRFIT—Multiple risk factor intervention trial

Risk factor changes and mortality results.

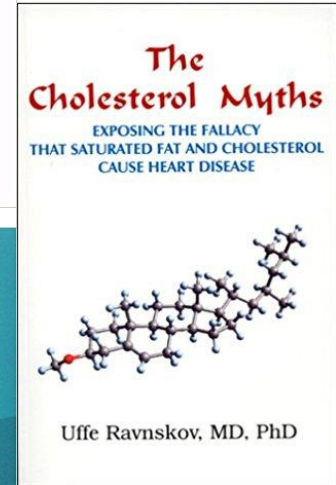
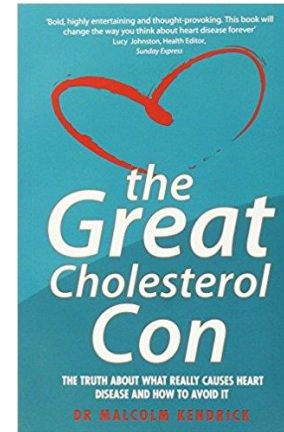
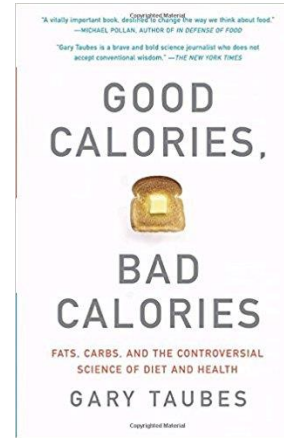
Multiple Risk Factor Intervention Trial Research Group. *JAMA*.1982;248(12):1465-77.

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## The Women's Health Initiative

Low-fat dietary pattern and risk of cardiovascular disease: Randomized Controlled Dietary Modification Trial.

Howard BV, Van Horn L, Hsia J, et al. *JAMA*. 2006;295:655-66.



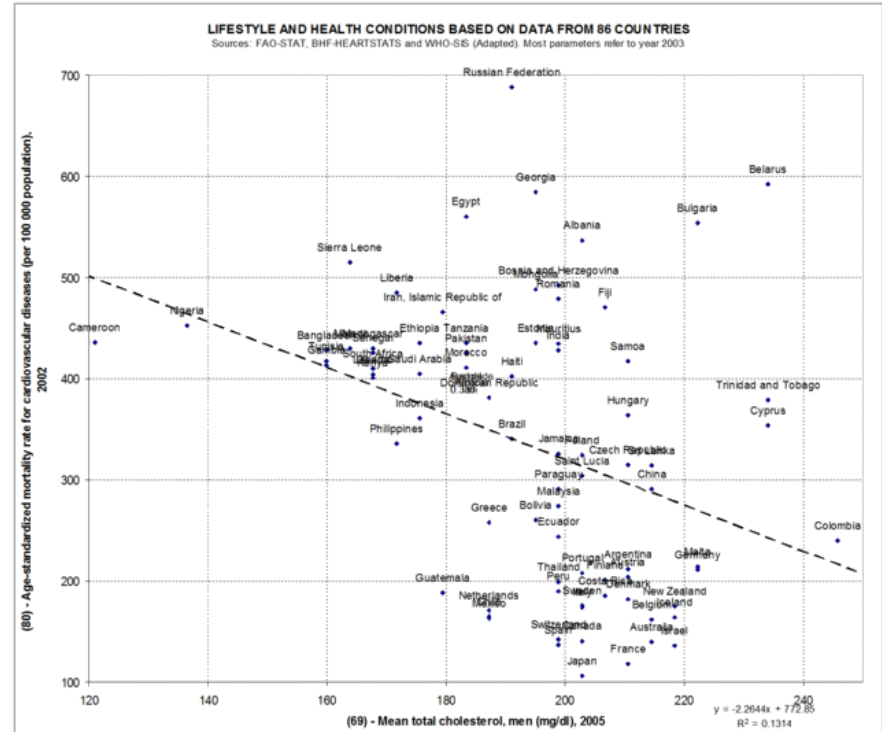


# Fat facts

- *Could it actually be that countries with higher cholesterol have lower incidence of CHD?*

*“It is now increasingly recognized that the low fat campaign has been based on little scientific evidence and may have caused unintended health consequences.”*

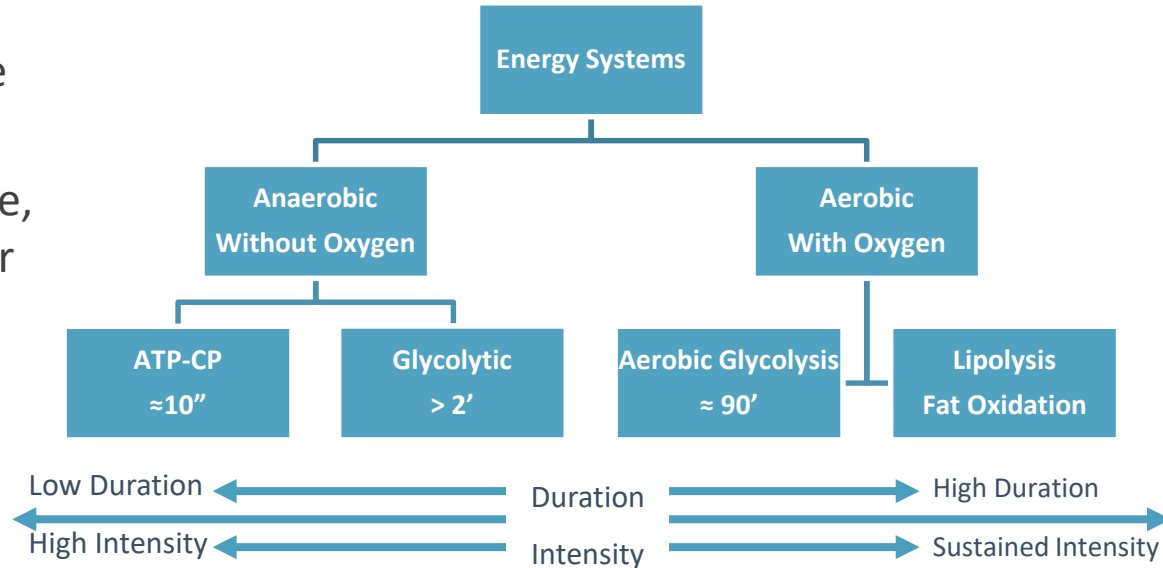
Drs. Frank Hu & Walter Willett, 2001, Harvard School of Public Health, Department of Nutrition



# Metabolic flexibility

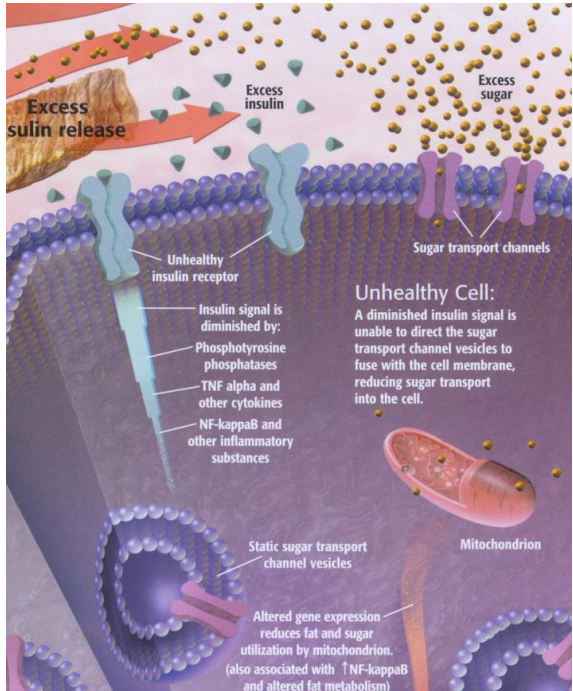
## Energy goes where energy flows (Kevin Hearon, D.C. , C.C.E.P.)

- The body will utilize or store energy
- What energy systems we use, in part, is determined by our metabolic flexibility
- How, What, When and Why we store energy is also determined by metabolic flexibility



# Insulin resistance leads to metabolic inflexibility

Energy goes where energy flows (Kevin Hearon, D.C. , C.C.E.P.)

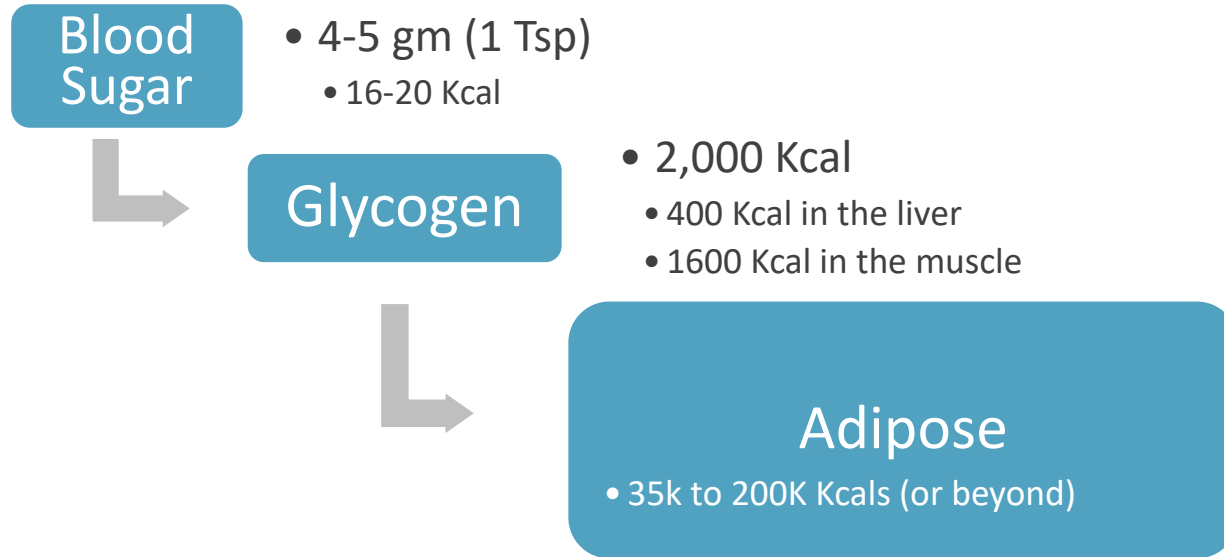


- A disorder of energy utilization and storage
  - Central obesity
  - Elevated blood pressure
  - Elevated fasting glucose
  - High triglycerides
  - High-oxidated LDLs
- Metabolic syndrome increases the risk of cardiovascular disease and diabetes
- Prevalence in the USA to be an estimated 34% of the adult population
- Prevalence increases with age

# Metabolic flexibility

Energy is burned or stored

Energy goes where energy flows (Kevin Hearon, D.C. , C.C.E.P.)



# Individuals experiencing joint discomfort

## Degenerative joint diseases

- Cartilage degradation, joint space narrowing, synovial inflammation, and bone changes (remodeling and formation of bone spurs)

Joint pain, swelling, stiffness

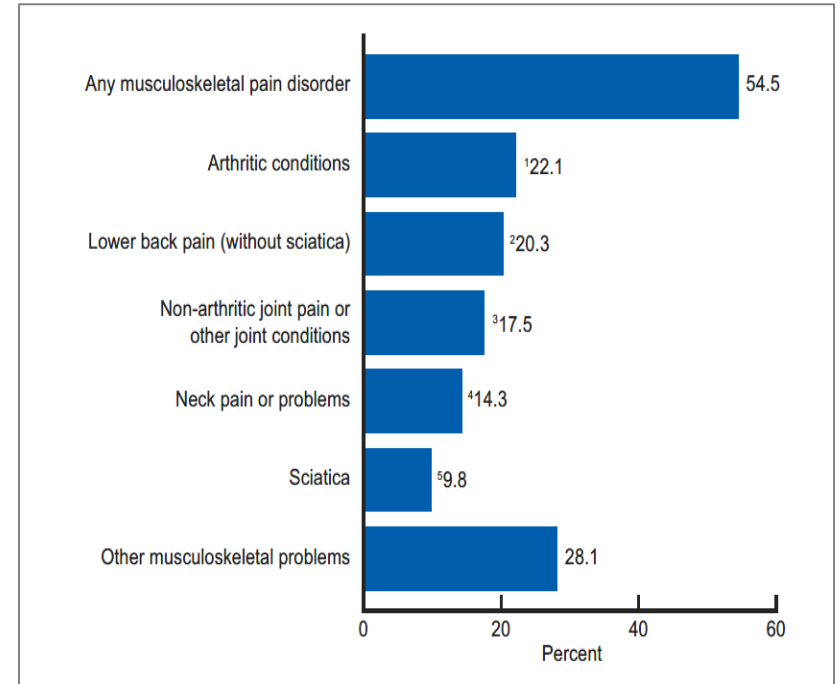
The most common types of arthritis affects  
~ 26.9 million adults in the US

Lawrence RC et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. *Arthritis & Rheumatism* 2008;58(1):26-35.  
Murphy L, Helmick C. The impact of osteoarthritis in the United States: a population-health perspective. *American Journal of Nursing* 2012;112(3):S13-19



# Musculoskeletal pain among adults

- 54.5% of U.S. adults (125 million) had a musculoskeletal pain disorder
- 20% of U.S. adults had arthritic conditions
- 22.1% Lower back pain
- 20.3% Non-arthritic joint pains
- 17.5% Neck pain or problems
- 14.3% Sciatica (9.8%)
- 28.1% Other musculoskeletal problem



Prevalence of musculoskeletal pain disorders among adults: United States, 2012

SOURCE: NCHS, National Health Interview Survey, 2012.

# Disability/Functional limitations

- **Leading Cause of Disability**

- Inflammatory rheumatic conditions are the most common cause of disability among US adults for the past 15 years

- **Work and Activity Limitation**

- Around 44% (23.7 million) report having activity limitations do to their rheumatism (2013-2015)

- **Functional Limitations**

- 2.5 times more likely to suffer a fall injury within 12 months compared with adults without arthritic pain

United States Bone and Joint Initiative: The Burden of Musculoskeletal Diseases in the United States (BMUS), Third Edition, 2014. Rosemont, IL. Available at <http://www.boneandjointburden.org> Accessed on April 19, 2014.

Barbour KE, Stevens JA, Helmick CG, Luo YH, Murphy LB, Hootman JM, Theis KA, Anderson LA, Baker NA, Sugerman DE. Falls and fall injuries among adults with arthritis—United States, 2012. *Morb Mortal Wkly Rep.* 2014;63(17):379-383

# Cost of treating rheumatic conditions

- Aggregate cost of treatment including the cost to society in the form of decreased or lost wages, is estimated to be
  - \$873.8 billion per year.
- Yet research dollars to identify causes, create new treatments, and reduce pain and disability remain much lower than that of other health conditions.
- With the aging of the US population, musculoskeletal diseases are becoming a greater burden every year.

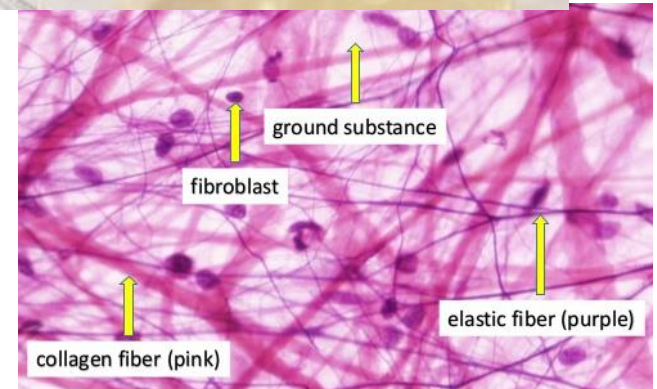
United States Bone and Joint Initiative: The Burden of Musculoskeletal Diseases in the United States (BMUS), Third Edition, 2014. Rosemont, IL. Available at <http://www.boneandjointburden.org>. Accessed on April 19, 2014



# Fascial anatomy

- **GROUND SUBSTANCE**

- Viscous, transparent fluid
- Surrounds all the cells in the body
  - “Internal ocean”
- Glycosaminoglycans (GAGS) or Mucopolysaccharide
  - Highly polar and attracts water
  - Polarity holds an electrical charge
  - Hyaluronic acid lubricates allowing glide
  - Proteoglycans form the gel
- Excellent at dispersing shock and holding tissues in place

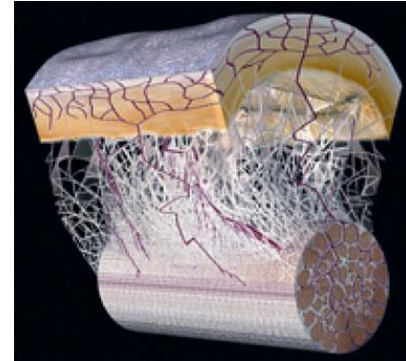
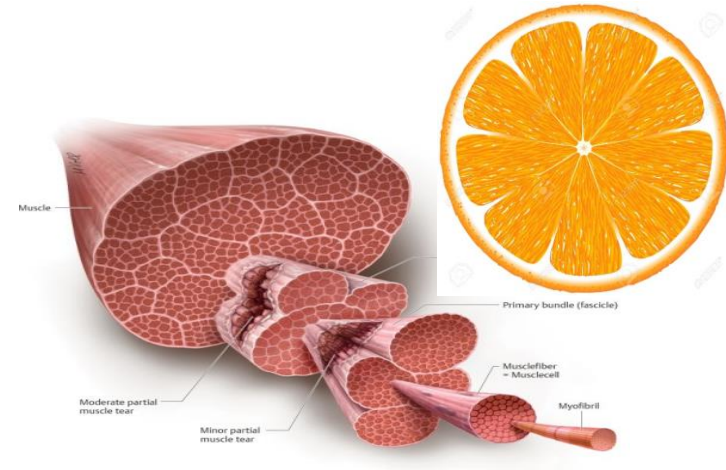


# Fascial anatomy

## THE GREAT ORGANIZER

- Fascial sheaths (which are hydrated and charged) surround and encapsulate fluid allowing nutrient exchange and waste elimination
- Fascia penetrates almost every structure in our bodies
- **Muscle > Tendon > Periosteum > Bone > Periosteum**
- **Tendon > Muscle > Tendon > Periosteum > Bone**
  - Connects the fascia in your toes to the fascia in your head
  - Uniting your body in one continuous fascial network

Chaudhry H, Schleip R, Ji Z, Bukiet B, Maney M, Findley T. Three-dimensional mathematical model for deformation of human fasciae in manual therapy. *J Am Osteopath Assoc.* 2008;108(8):379-90.



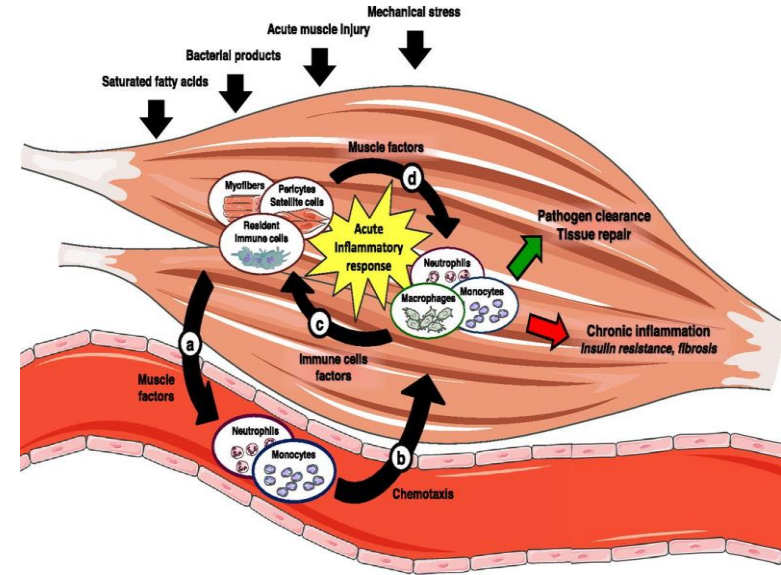
# Fascial anatomy

- **GROUND SUBSTANCE**
  - Thixotropy
    - Ability to go from a gel to a liquid state
    - Like Jell-O, when cool, it's jelly and when its warm, it's a thick liquid
  - Mechanical stretch, body heat and bio-electric energy all contribute to keeping ground substance a liquid
    - Liquid state allows:
      - Movement and stretch
      - Exchange of nutrients and cellular wastes removal
  - Hardened tissue lacks glide and damages tissue
    - Initiating an inflammatory response



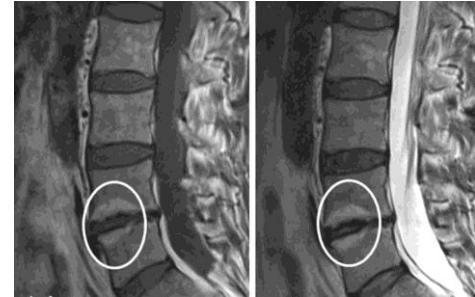
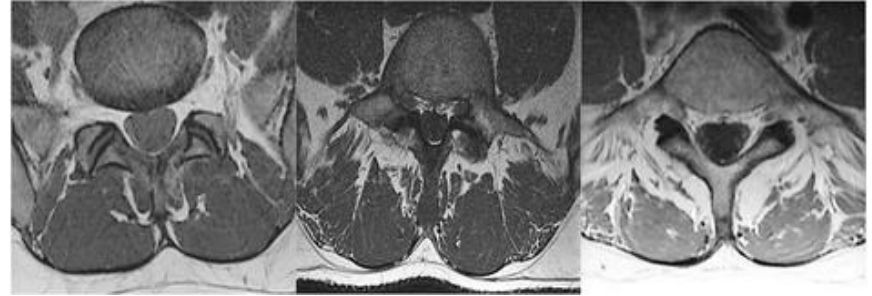
# Injury and inflammatory response

- Cell walls damaged and releases inflammatory signals
- Responsible for the recruitment of immune cells
- This leads to the acute inflammatory response necessary for pathogen clearance and tissue repair



# Fat is a metabolic and mechanical disorder

- Metabolically inflexible tissue becomes chronically inflamed
- Lipid accumulation deposits in damaged tissue
- Fatty infiltrated tissue is weaker and is prone to re-injury and microtrauma
- Creating a perpetual cycle of disease



Fat infiltration of paraspinal muscles is associated with low back pain, disability, and structural abnormalities in community-based adults. *The Spine Journal*. 2015;15(7):Volume 15:1593–1601.

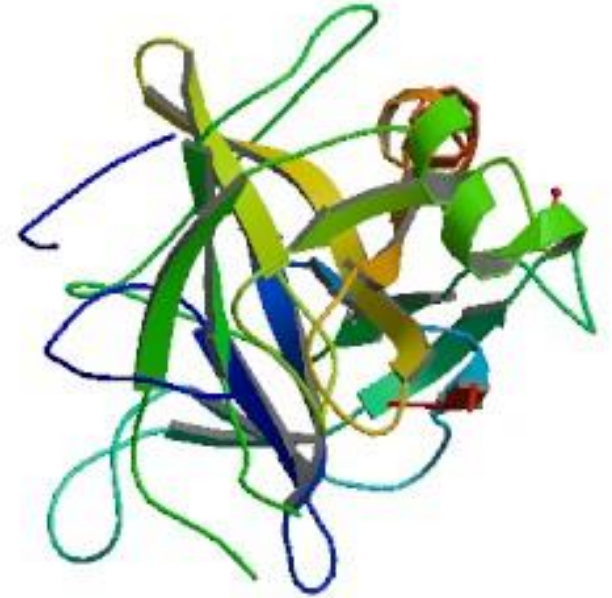
# Common medications for joint and myofascial pain

- Acetaminophen
  - Hepatotoxicity (acute liver failure)
- NSAIDs
  - Ibuprofen
    - GI toxicity (GI bleeding and ulcers)
  - Naproxen, Celecoxib
    - Cardiovascular, cerebrovascular events
    - Kidney toxicity
- Opioids
  - Epidemic addictions



# Proteolytic enzymes

- Proteolytic enzymes
  - Protein splitting
  - Inflammatory chemicals are bound to protein
- Assist in degradation of damaged and dead tissue
- Limits excess clotting of vessels in the injured tissues
- Reducing viscosity of extracellular fluid, thereby maintaining more normal circulation
- Allows for enhanced nutrient delivery and waste removal



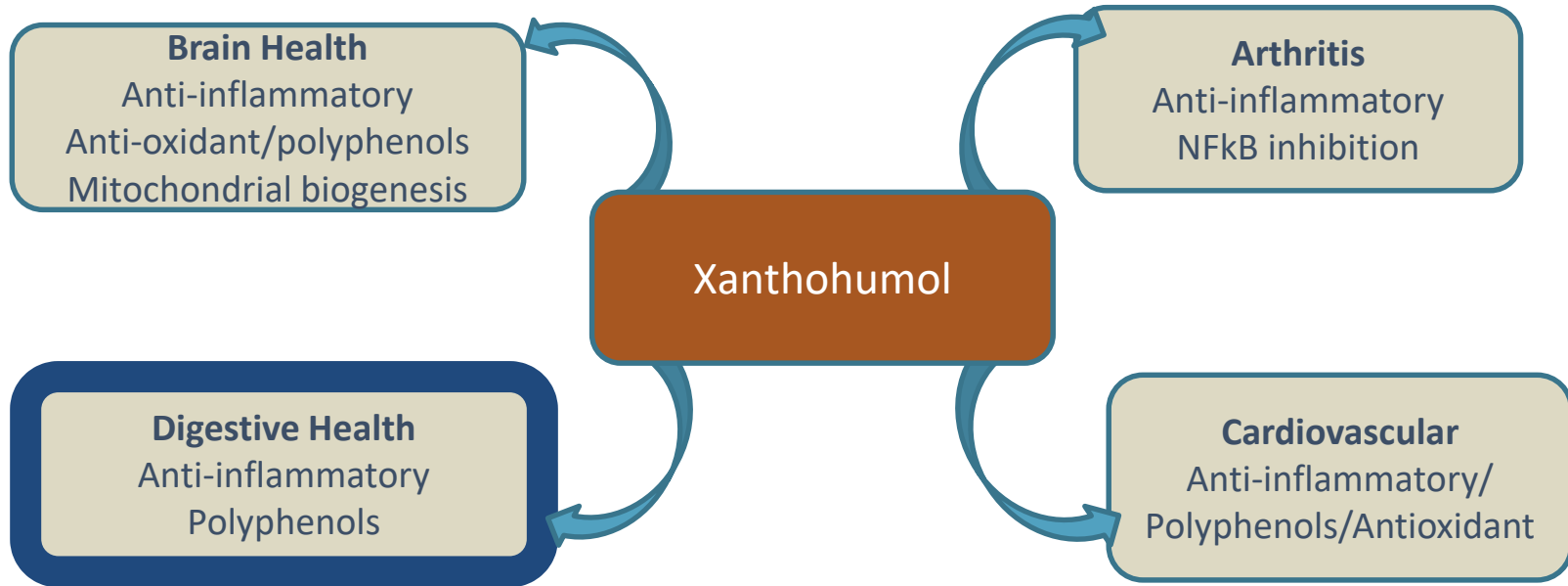
<https://en.wikipedia.org/wiki/Chymotrypsin>



# Xanthohumol: strong clinical data

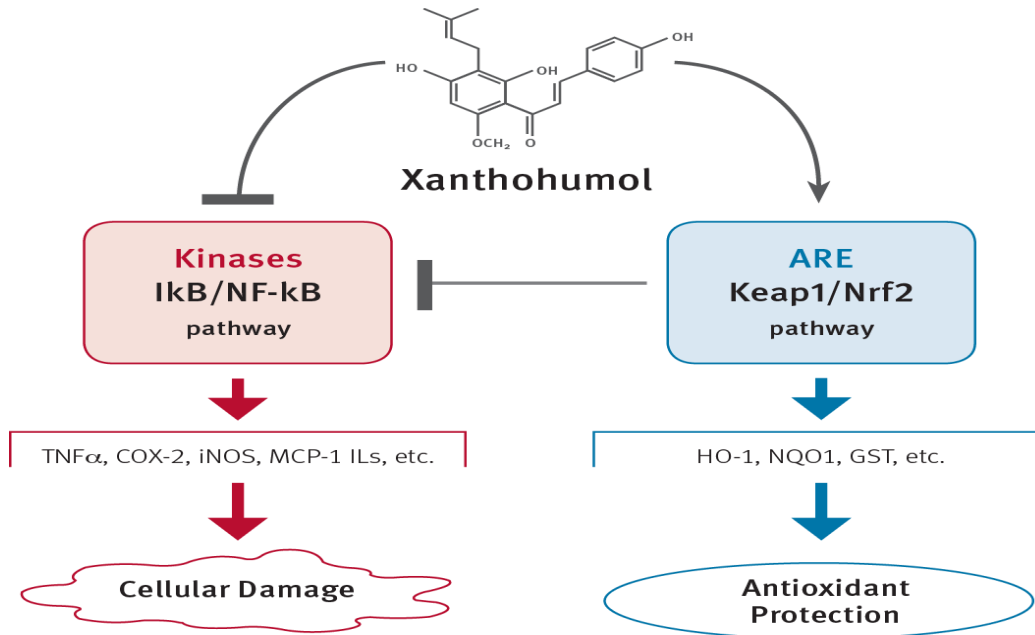
## Next generation Skrm technology

**Excellent science: >250 publications in preclinical science**





# Xanthohumol modifies kinases in favor of antioxidant protection



# Bioavailable form of curcumin

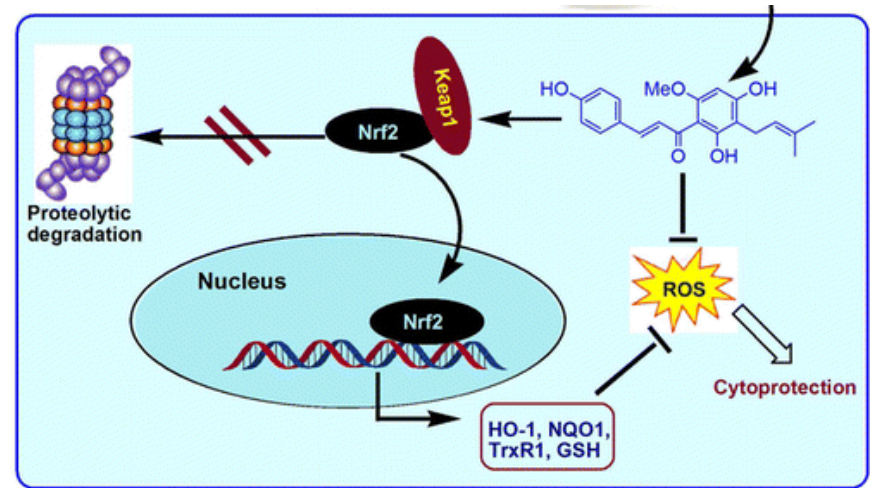
- Shows potent anti-inflammatory activity—may help reduce inflammation-signaling molecules, such as NF- $\kappa$ B, TNF- $\alpha$ , COX-2, and PGE<sub>2</sub><sup>1</sup>
- Shows potent antioxidant activity – may help improve overall redox status through influencing antioxidants Nrf2, HO-1, and NQO1<sup>2</sup>
- Delivers significant concentrations of biologically active free curcuminoids—regarded as major limitation for efficacy of curcumin supplementation<sup>2</sup>
- Blend of stable curcuminoid and galactomannan compound (from fenugreek) designed for great bioavailability and more reliable clinical outcomes



1. Vecchi Brumatti L, Marcuzzi A, Tricarico PM, Zanin V, Giradelli M, Bianco AM. Curcumin and inflammatory bowel disease: potential and limits of innovative treatments. *Molecules*. 2014;19(12):21127-21153.
2. Rajasekaran SA. Therapeutic potential of curcumin in gastrointestinal diseases. *World J Gastrointestinal Pathophysiology*. 2011;2:1-14. 35. González-Reyes, S. Guzmán-Beltrán S, Medina-Campos ON, Pedraza-Chaverri J. Curcumin pretreatment induces Nrf2 and an antioxidant response and prevents hemin-induced toxicity in primary cultures of cerebellar granule neurons of rats. *Oxid Med Cell Longev*. 2013;2013:801418
3. Krishnakumar IM, Abhilash M, Gopakumar G, Dinesh K, Balu M, Ramadasan K. Improved blood–brain-barrier permeability and tissue distribution following the oral administration of a food-grade formulation of curcumin with fenugreek fibre. *Journal of Functional Foods*. 2015;14:215-225.

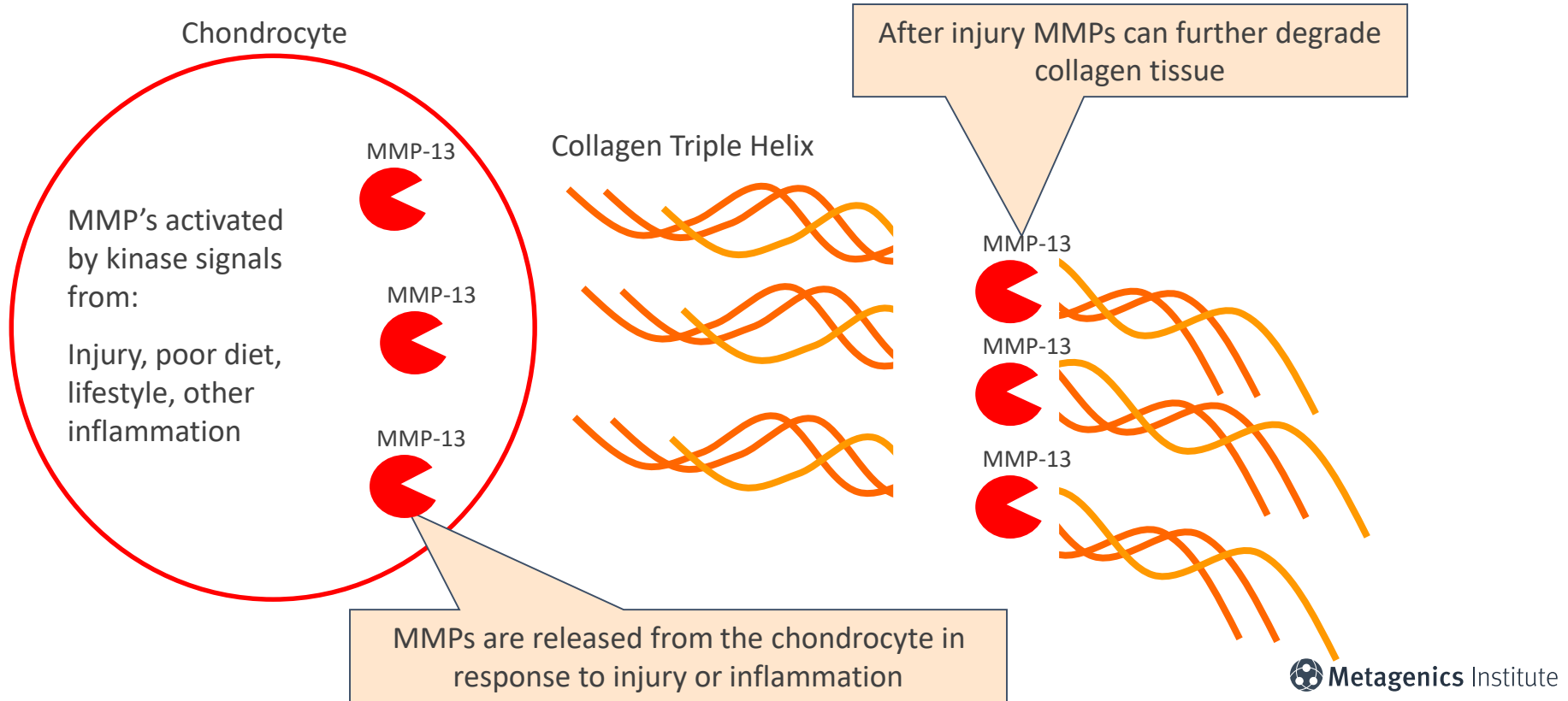
# Xanthohumol (Xn): neuroprotective against oxidative-stress

- Xns  $\alpha,\beta$ -unsaturated ketone structure activates transcription factor Nrf2, a key determinant for cytoprotection
- Upregulates phase II cytoprotective genes and gene regulating products
- Xn is an activator of Nrf2 in neuronal cells
  - Suggest Xn may be a candidate for the prevention of neurodegenerative disorders



Adapted with permission from Yao J et al. *J. Agric. Food Chem.* 2015;63 (5):1521–1531. DOI: 10.1021/jf505075n

# Matrix metalloproteinase (MMP) enzymes digest collagen and connective tissue



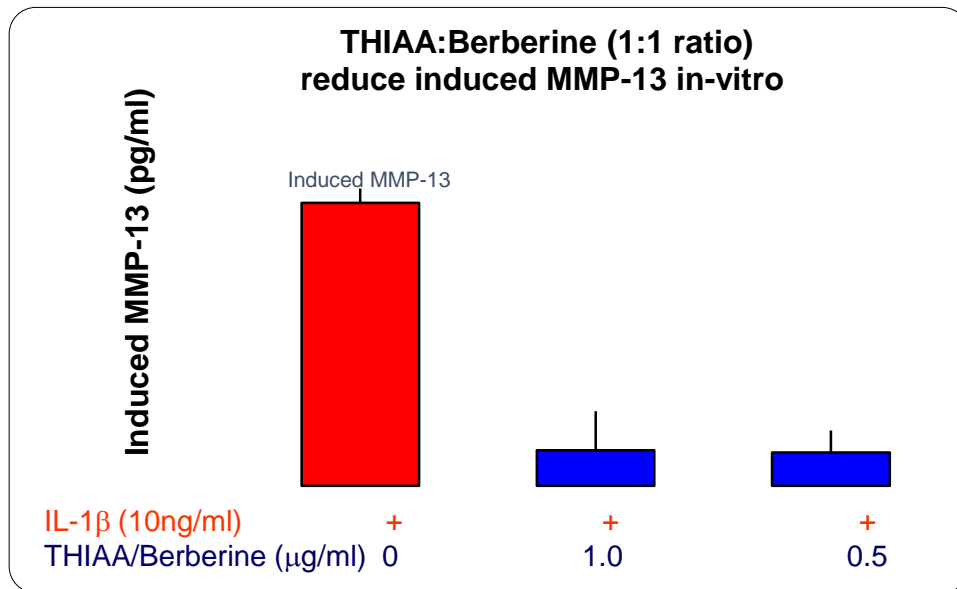
# Modulating matrix metalloproteinase enzymes

## The power of synergy:

Berberine & THIAA reduced MMP-13 by 87.3%

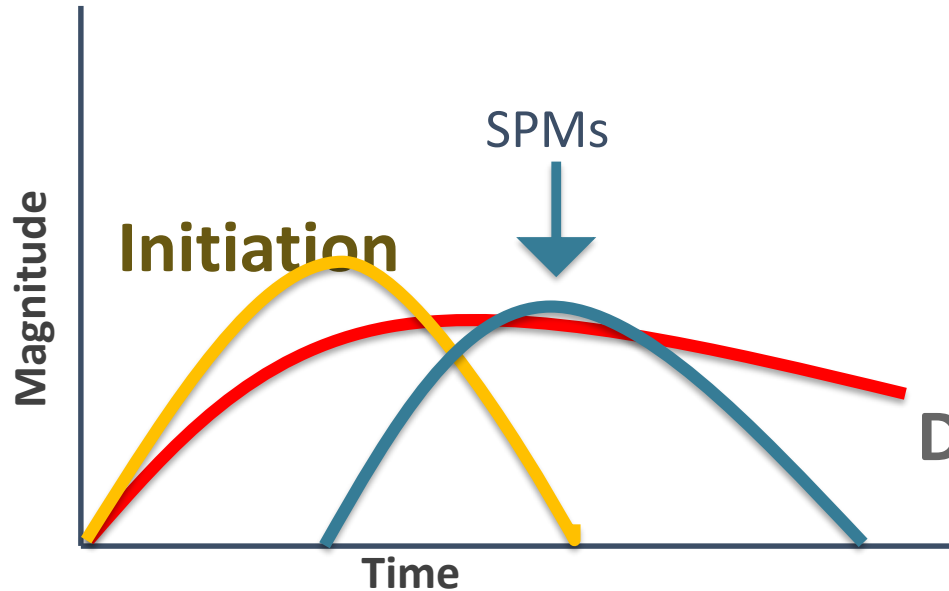
Significantly more than either nutrient alone\*

- THIAA 34.9% reduction
  - Tetrahydro-iso-alpha acids
- Berberine 75.2% reduction



\*Data from In-vitro IL-1β Activated MMP-13 Expression in SW1353 cells

# Specialized pro-resolving mediators (SPMs)



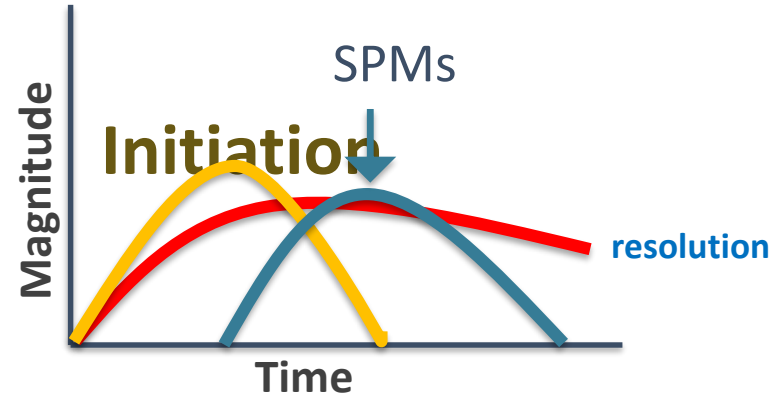
SPMs act to *resolve* inflammation. Without resolution, even a reduced inflammatory response can become chronic, and full healing and return to homeostasis cannot occur

**Deficient Resolution**

*Balance* between **initiation** and **resolution** is critical

# Specialized pro-resolving mediators (SPMs)

- Stimulates clearance of neutrophil and leukocyte pro-inflammatory signals
- Reduction of cytokines, chemokines, MMP2 and MMP9
- Pro-resolving actions are infection protective
  - Identified in self resolving exudates during active *E.coli* infection



Balance between **initiation** and **resolution** is critical

Serhan CN. *Nature*. 2014;510:92-101

Spite et al. *Cell Metab*. 2014;19(1):21-36

# Supporting weight management in clinical practice



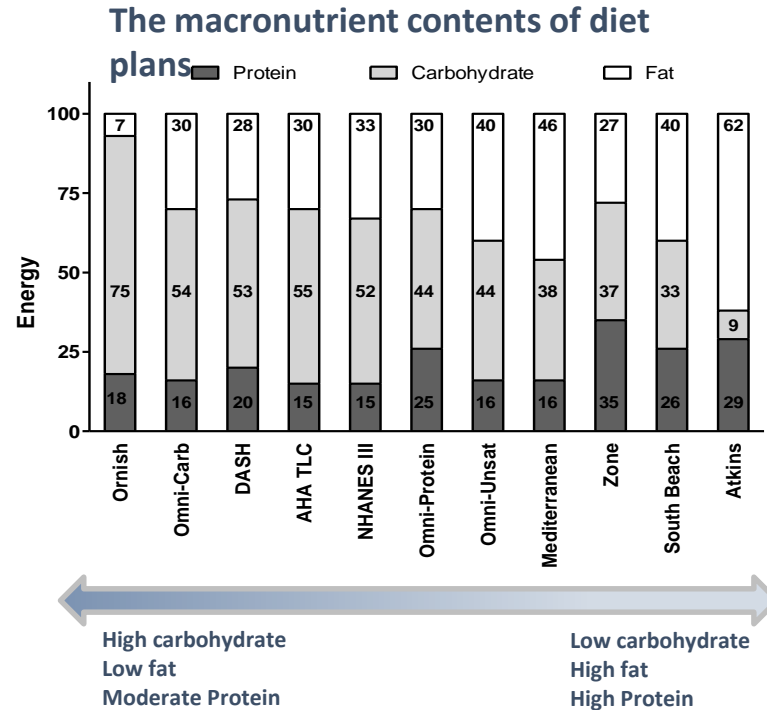
# One diet doesn't fit all:

## Diets with different compositions of fat, protein, and carbohydrates

- Different diets varying in their fat, protein, and carbohydrate composition have been shown to successfully support weight loss and benefit cardiovascular disease and diabetes<sup>1</sup>
- **Diets that are tailored** to the patient's metabolic and health status, as well as personal and cultural preferences, may have the best chance for long-term success

**The best diet is one that you can stick with for the long-term. Any lifestyle modification should be closely monitored and modified as needed**

1. Sacks et al. *The New England Journal of Medicine* 2009; 360(9): 859–873



Adapted from: de Souza et al. *The American Journal of Clinical Nutrition* 2008; 88(1): 1–11

# The challenge of weight maintenance over time

- Despite benefits of weight loss to overall health, only 1 in 6 overweight or obese US adults report ever having successfully maintained weight loss of at least 10% for 1 year<sup>1</sup>
- Health records for 76,704 obese men and 99,791 obese women examined over 9 year period in UK.<sup>2</sup>
  - **5% body weight loss over 9 year period\***
    - 1 in 12 men and 1 in 10 women with simple obesity (BMI 30-35kg/m<sup>2</sup>) lost 5% body weight
  - **Weight regain\***
    - Over the 9 years examined, only 14% of men and 15% of women showed reduction in BMI category without increases over the follow-up period
- Slow weight gain over time identified in prospective study: Helsinki Health Study.<sup>3</sup>
  - 30% of the normal middle-aged population gained at least 11lbs over the 5-7 year study period

1. Kraschnewski et al *Int J Obes* 2010;34:1644-54

2. Fildes et al., *Am J Public Health*. 2015;105(9):e54–e59

3. Loman et al., *BMC Public Health* 2013;13:259

# What happens after weight loss?

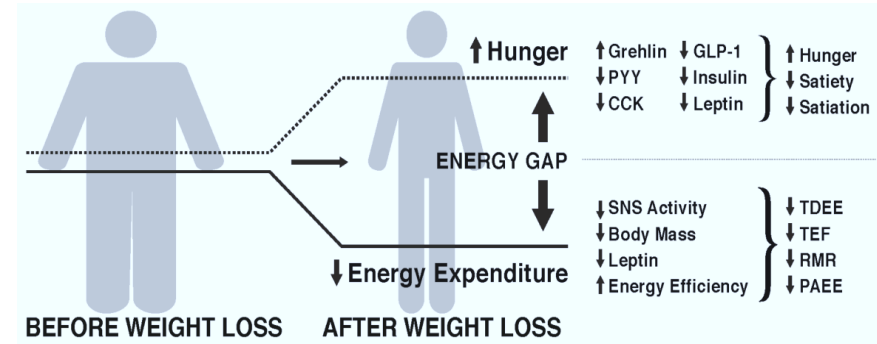
## Factors favoring weight regain

- **Compensatory physiological adaptations:**

- ✓ Changes in circulating appetite-related hormones
- ✓ Reduction of metabolic rate (less energy required to maintain a lower body weight)
- ✓ Adaptive alterations in nutrient metabolism
- ✓ Subjective appetite, craving (*hedonic reward systems*)

- **'Obesogenic' environment**

- ✓ Opportunities to overeat on a regular basis.

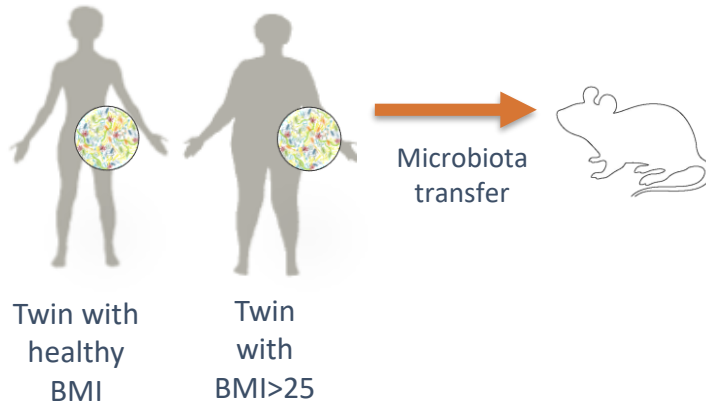


- ➔ Powerful counter-regulatory “homeostatic” mechanisms driving **weight regain**
- ➔ The most important component of an effective weight-management program must be the prevention of unwanted weight regain

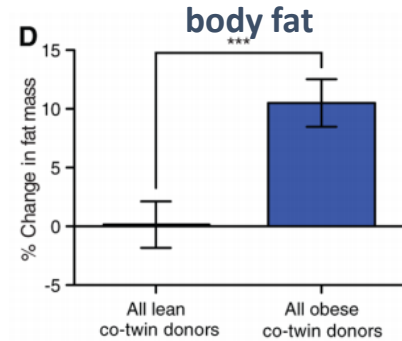
1. GreenWay FL, *International Journal of Obesity* (2015) 39, 1188–1196
2. Sumithran et al., *N Engl J Med* 2011;365:1597-604
3. Leibel et al (1995) *NEJM* 332:621-628

# Differences in the microbiome may promote body fat mass accumulation

Microbiome samples were taken from twins



When the microbiome samples were transferred to mice, those receiving the microbiome sample from overweight twin gained significant

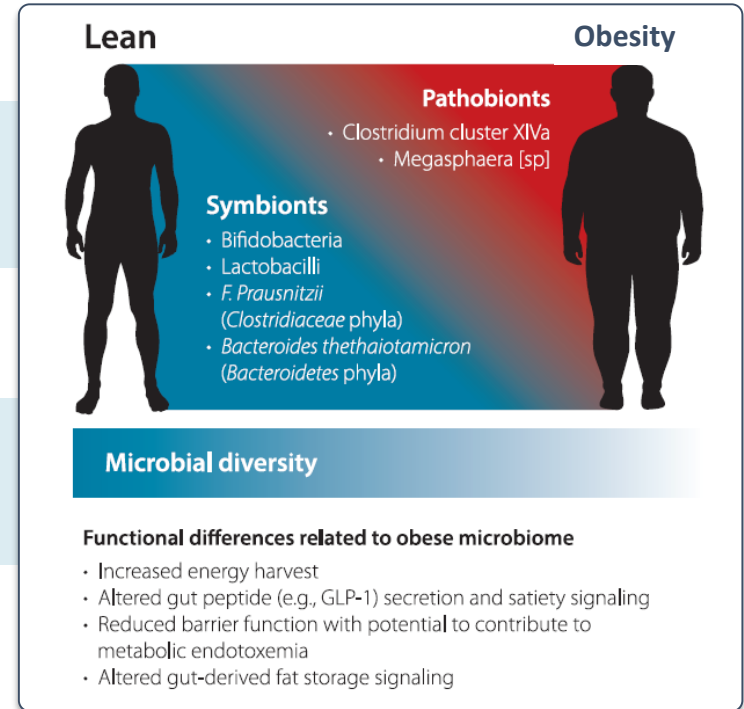


# Microbiome and body mass regulation— what is the evidence?

Microbiota commonly identified in samples from lean and obese individuals differ

A less diverse microbial community has been identified in obesity

Differences in expression of pathways related to body mass regulation has been shown in some studies to differ between lean and overweight microbiome samples

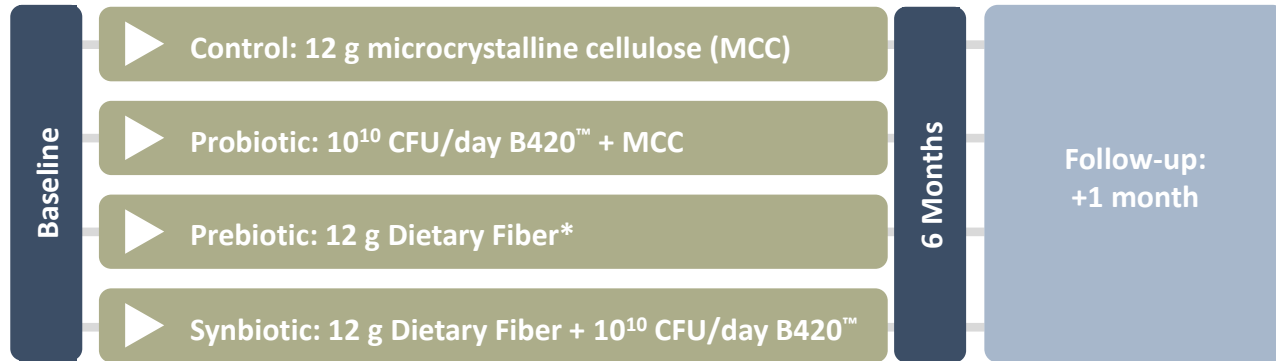


Boulangé et al. *Genome Medicine*, 2016;8:42  
Walters et al., *FEBS Lett.* 2014;588(22): 4223–4233  
Ridaura et al. *Science*. 2013;341(6150)  
Turnbaugh et al., *Nature*. 2009; 457(7228): 480–484  
Turnbaugh et al., *Nature*, 2006;444(7122):1027-31

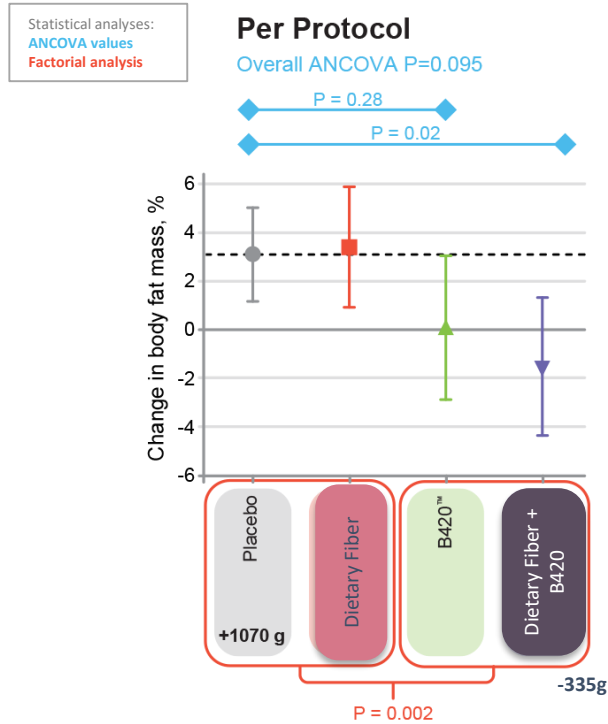
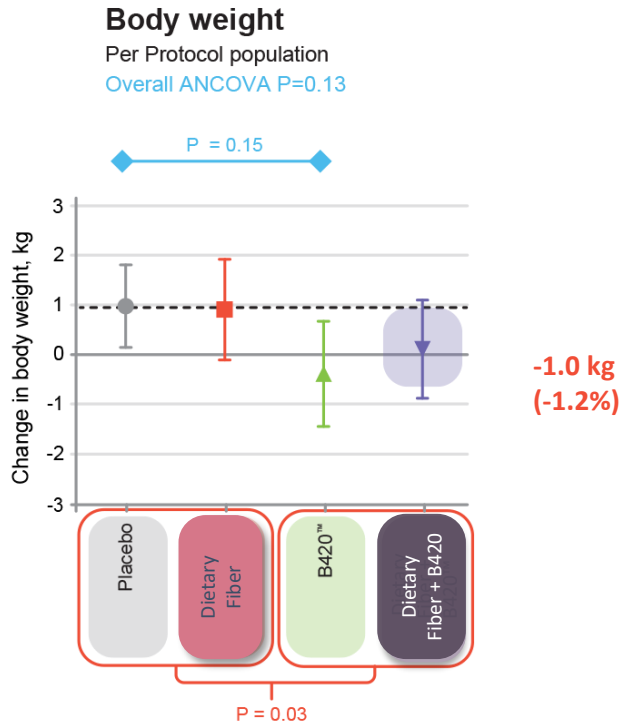
# *Bifidobacterium animalis* ssp. *lactis* 420

## Clinical data— study design and study population

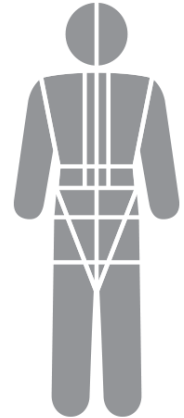
- Randomized, double-blind, multicenter study
- Study design and execution follows ICH-GCP
- 225 Finnish participants with BMI 28-34.9, otherwise healthy (~75% women)
- Primary outcome: relative change in body fat mass



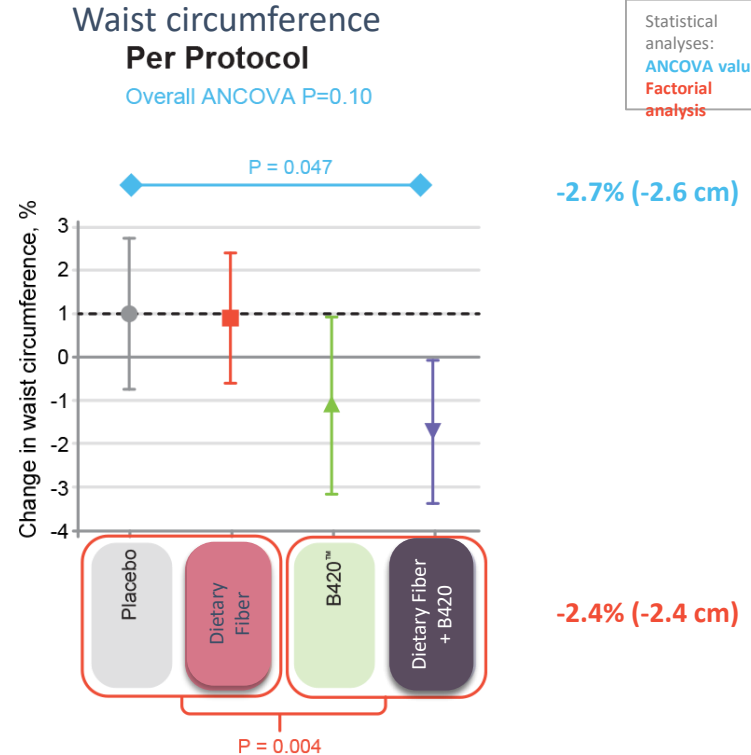
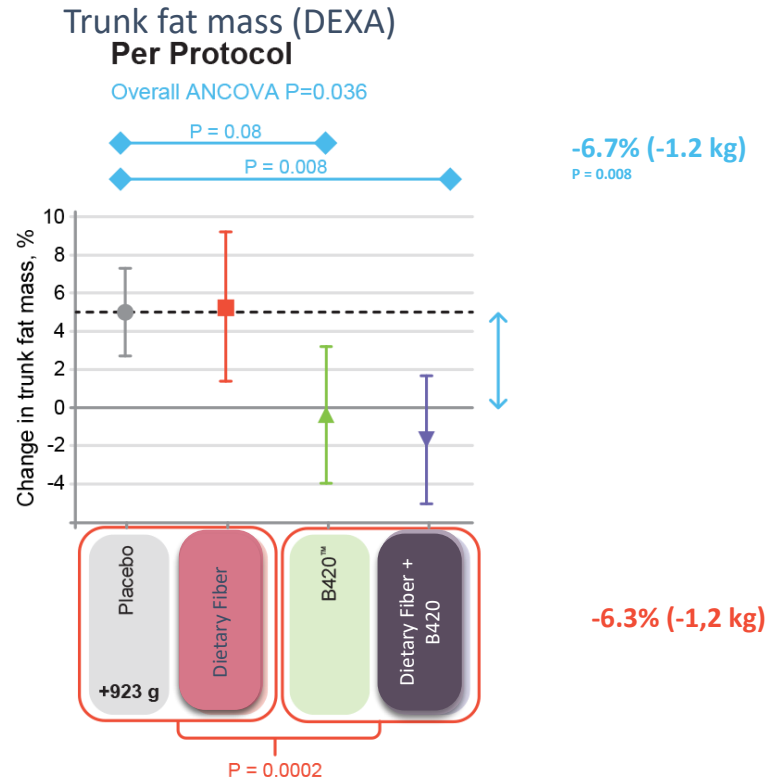
# Results: Reduction of body weight and total body fat mass compared to placebo



**-4.5% (-1.4 kg)  
in fat mass**  
P=0.02

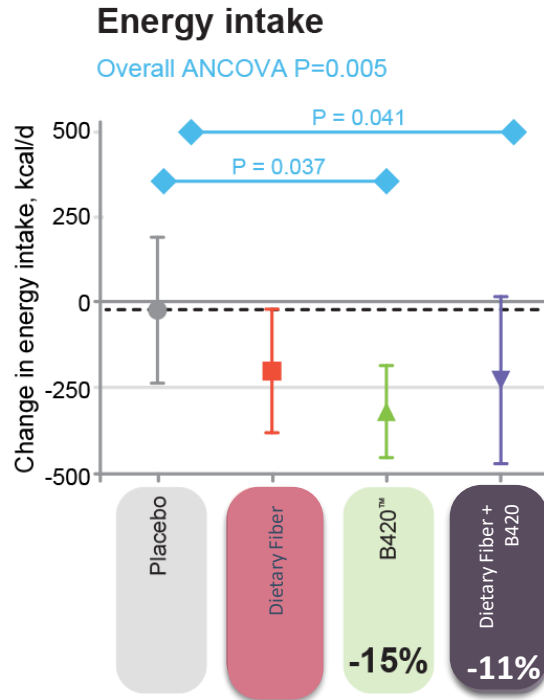


# ... which was localized to trunk fat mass





# *Bifidobacterium animalis* ssp. *lactis* 420 alone or in combo with dietary fiber reduces energy intake



Data from 5-day food diaries, Per Protocol population

# Summary: *Bifidobacterium animalis* ssp. *lactis* 420 clinical results

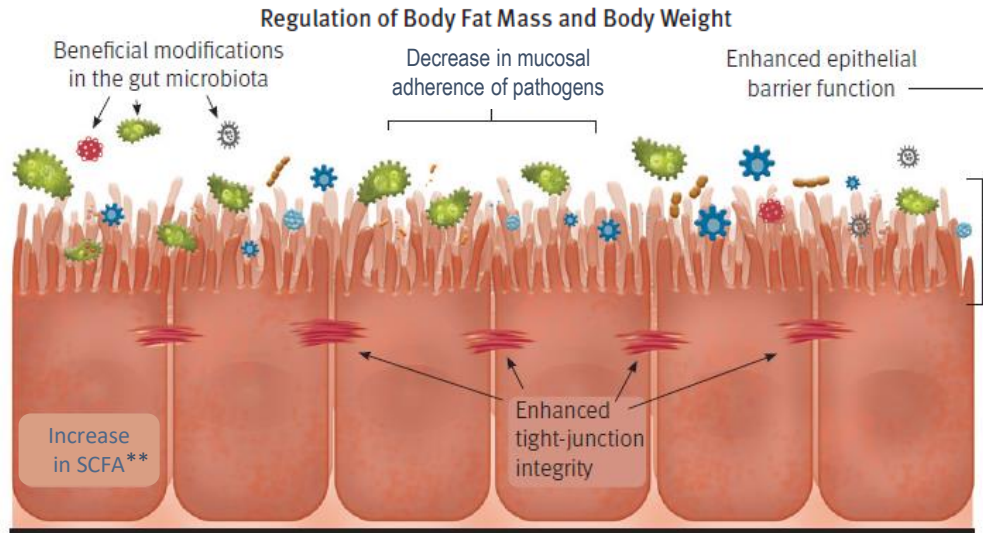
	B. lactis 420	B. lactis 420 + Dietary Fiber
Has a weight management benefit	✓	✓
Reduced body fat mass	✓	✓
Increased lean mass		✓
Reduced energy intake	✓	✓
Reduced trunk fat mass	✓	✓
Reduced waist circumference	✓	✓

\* As compared to placebo

Changes seen with no lifestyle alteration—no increase in exercise (reported—metabolic equivalents). No major adverse events and no difference across study groups, no differences in safety measures across groups and no major changes from baseline.

# *Bifidobacterium animalis* ssp. *lactis* 420: Potential mechanisms of action

All of the actions below are supported by pre-clinical and clinical data with B-420™<sup>1-5</sup>



• Decreased bacterial and LPS\* translocation

\*LPS- Lipopolysaccharide  
\*\*SCFA- Short Chain Fatty Acids

1. Putaala et al., *Res Microbiol* 2008;159(9-10):692-698
2. Amar et al., *EMBO Mol Med* 2011;3(9):559-572
3. Stenman et al., *Beneficial Microbes*, 2014;5(4):437-445

4. Stenman et al., *Diabetol Metab Syndr* 2015;12(7):75
5. Stenman et al., *EBioMedicine*. 2016;13:190-200

# Summary and conclusions



- Long-term management of body weight and maintenance post weight loss continues to be a challenge
- Over the past decade, increasing evidence links the intestinal microbiome with regulation of body weight and body fat mass
- Clinically studied, precision probiotics offer an opportunity to harness the link between the intestinal microbiome and health– and genus, species, and strain specificity is key
- Pre-clinical work with the probiotic strain *Bifidobacterium lactis* 420 showed that this probiotic strain has beneficial impact on intestinal barrier function, satiety signaling and body weight and body fat regulation
- Clinical study with this strain highlighted improved body weight and food intake regulation over 6 months in supplemented individuals

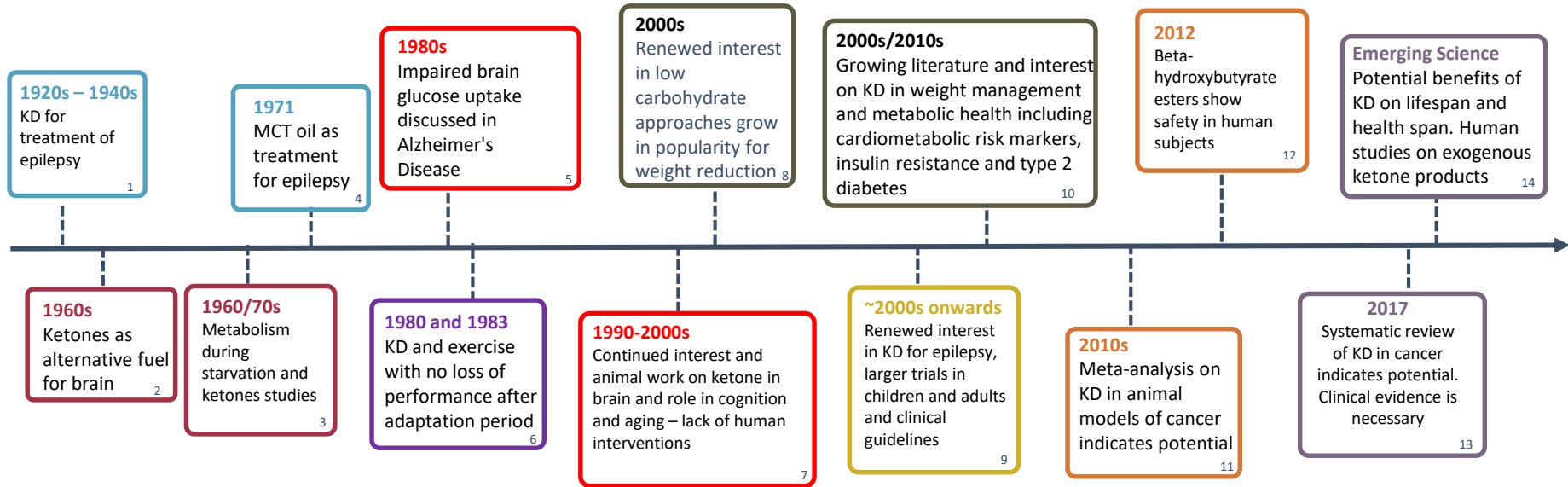
# What are some practical applications that can help your patients to lose weight and prevent weight regain?

- What has been shown to work (e.g. ketogenic diets)
- Focus on underlying factors and support the patient during weight loss from a holistic health stand-point
- Dietary approaches—for loss and long-term maintenance (homoeostatic and physiological approaches)
- Practice approaches—how often to see them (nutritional counseling and social support to influence an individual's motivation and perseverance), how long is the weight maintenance phase
- Use of tools such as meal-replacements, and technological advances in smartphone applications increase **the cost-effectiveness** of behavioral strategies.



# Ketogenic diet: One approach to weight management

# Evolution of ketogenic diets (KD)



1. Wheless JW *Epilepsia* 2008; Suppl 8:3-5

2. Owen OE et al. *The Journal of Clinical Investigation* 1967; 46(10):1589-95

3. Cahill GF. *Annual Review Nutrition* 2006; 26:1-22

4. Huttenlocher PR et al. *Neurology* 1971; 21(11):1097-103

5. Hoyer et al. *Journal of Neurology*. 1988; 235:143-148

6. Phinney SD et al. *Metabolism* 1983; 32(8):757-68

7. Kashiwaya et al. *PNAS* 2000; 97(10):5440-44

8. Volek & Westman. *Cleveland Clinic Journal of Medicine* 2002;69(11):849, 853

9. Lefevre et al. *Pediatrics* 2000; 105(4):e46

10. Paoli et al. *European Journal of Clinical Nutrition* 2013; 67:789-796

11. Seyfried T et al. *Biochemistry Biophysics Acta* 2011; 1807(6):577-94

12. Clarke K et al. *Regul Toxicology Pharmacology* 2012; 63(2)

13. Erickson N et al. *Medical Oncology* 2017; 34(5):72

14. Newman JC et al. *Cell Metabolism* 2017; 26: 547-57

# Ketosis and the ketogenic diet

- **What are ketone bodies and how are they produced?**

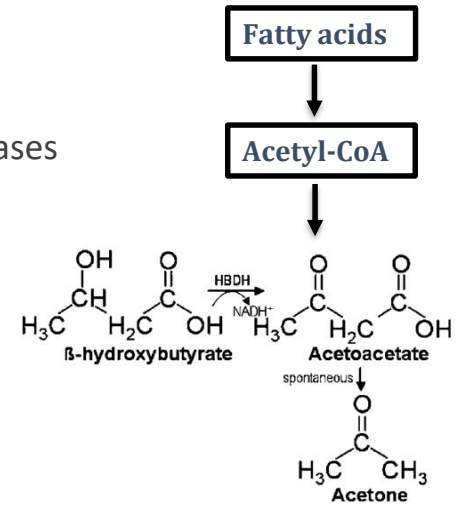
- Ketone bodies production in the liver is a natural process when the body increases the breakdown of fat during a fasting state and/or prolonged exercise as the main source of fuel.
- The main endogenous ketone bodies are acetone, acetoacetate and beta-hydroxybutyrate (BHB).

- **What is ketosis?**

- When ketone bodies accumulate in the bloodstream (>0.5 mmol/L) due to low glucose availability, they cause a metabolic state called ketosis.
- The most efficient approach that result in nutritional ketosis is to lower dietary carbohydrate intake while increasing fat intake.

- **What is a ketogenic diet?**

- Low carbohydrate (<50g)
  - High fat (generally ~70% energy)\*
  - Adequate protein (~20% energy)\*
- Some clinical indications require more strict adherence e.g. epilepsy
    - \* Depending on overall kcal intake and physical activity



1. Prins ML, J Cereb Blood Flow Metab, 2008; 28(1):1-16

2. Paoli A, et al, *European Journal of Clinical Nutrition*, 2013, 67, 789–796

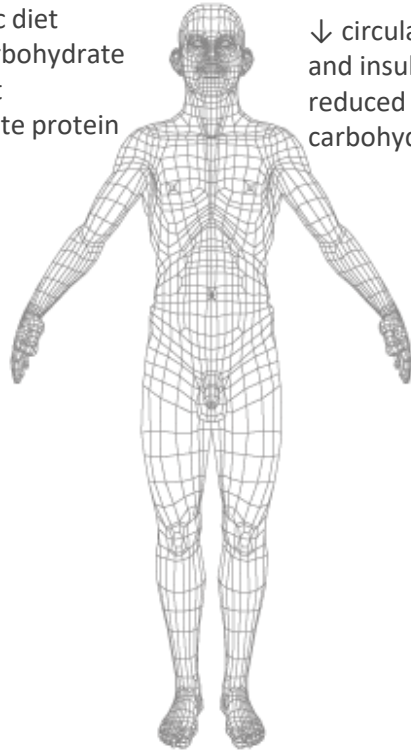


# The metabolic adaptation (keto-adaptation) that occurs with a ketogenic diet

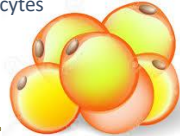
Ketogenic diet

- Low carbohydrate
- High fat
- Adequate protein

↓ circulating glucose and insulin due to reduced dietary carbohydrate intake



↑ lipolysis and ↑ release of FFA and glycerol from adipocytes



FFA

Glycerol

glucose

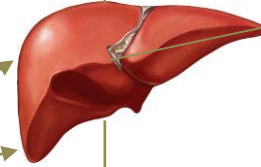
FFA



↑ use of FFA as energy source in skeletal muscle with preservation of glycogen stores



↑ ketone body (bHB, acetone, acetoacetate) in circulation and utilization by brain as fuel source

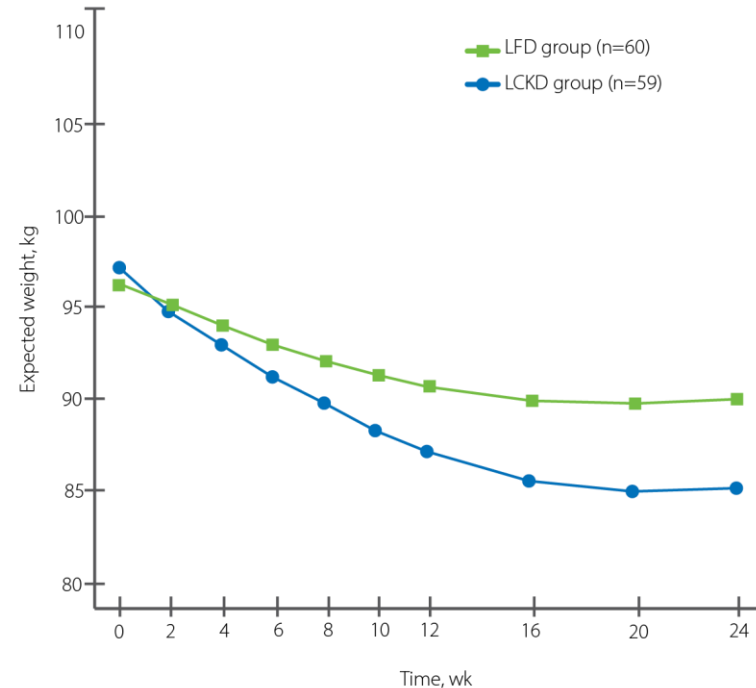


↑ production of ketone bodies using fatty acids (from dietary source and release from adipose tissue) for ketone body production within liver mitochondria



# Can ketogenic diets be used for weight management?

- In subjects with BMI  $>30\text{kg/m}^2$ , intervention with:
  - LCKD: Energy-reduced, low-carbohydrate ketogenic diet or
  - LFD: Low-fat diet
- Over 24 weeks, the change in body weight was  $-12.0\text{ kg}$  (95% CI,  $-13.8$  to  $-10.2\text{ kg}$ ) in the LCKD group compared with  $-6.5\text{ kg}$  (95% CI,  $-8.4$  to  $-4.6$ ) in the LFD group
- **61% of recipients on LCKD lost  $>10\%$  of their initial body weight at 24-weeks**



Adapted from: Yancy et al. *Annals of Internal Medicine* 2004;140(10):769-777

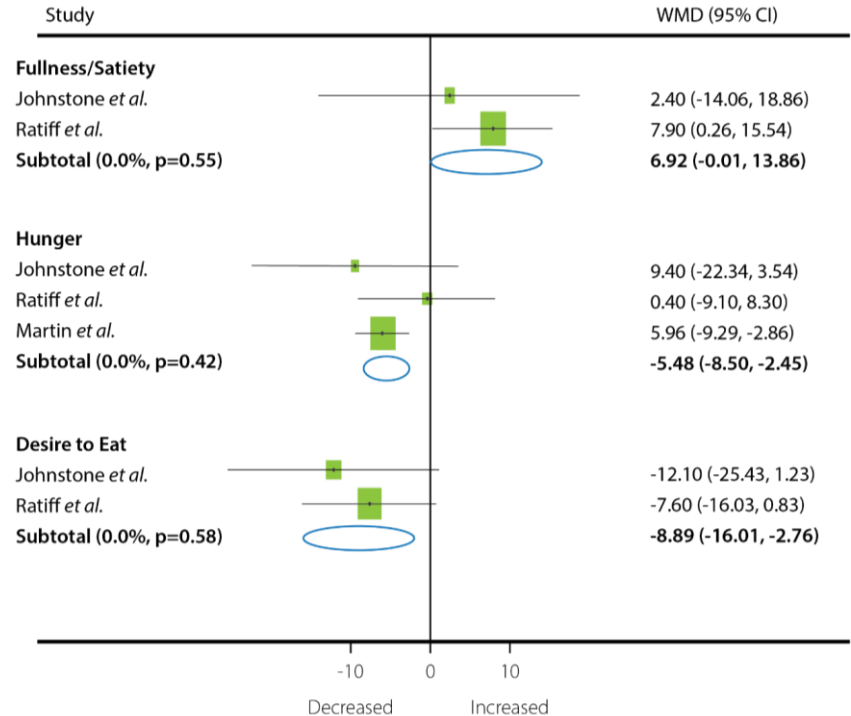
# Change in appetite in response to ketogenic low- carbohydrate diet

## Method

- Systematic review and meta-analysis of ketogenic diets
- Primary outcome assessed was subjective measures of appetite using visual analogue scale (VAS) data

## Conclusions

- ***Individuals following ketogenic diet were significantly less hungry and had reduced desire to eat when compared with baseline values. Furthermore, there was no significant increase in hunger following ketogenic diet.***
- **This may help facilitate adherence to lower kcal intakes**



Adapted from: A. A. Gibson *et al.* *Obesity review* 2015; 16(1): 64–76

# The effectiveness of ketogenic diet to combat the adverse metabolic pathologies of obesity

30 adults diagnosed with MetS — randomly assigned to one of 3 groups — 10 wk

Sustained ketogenic diet no exercise

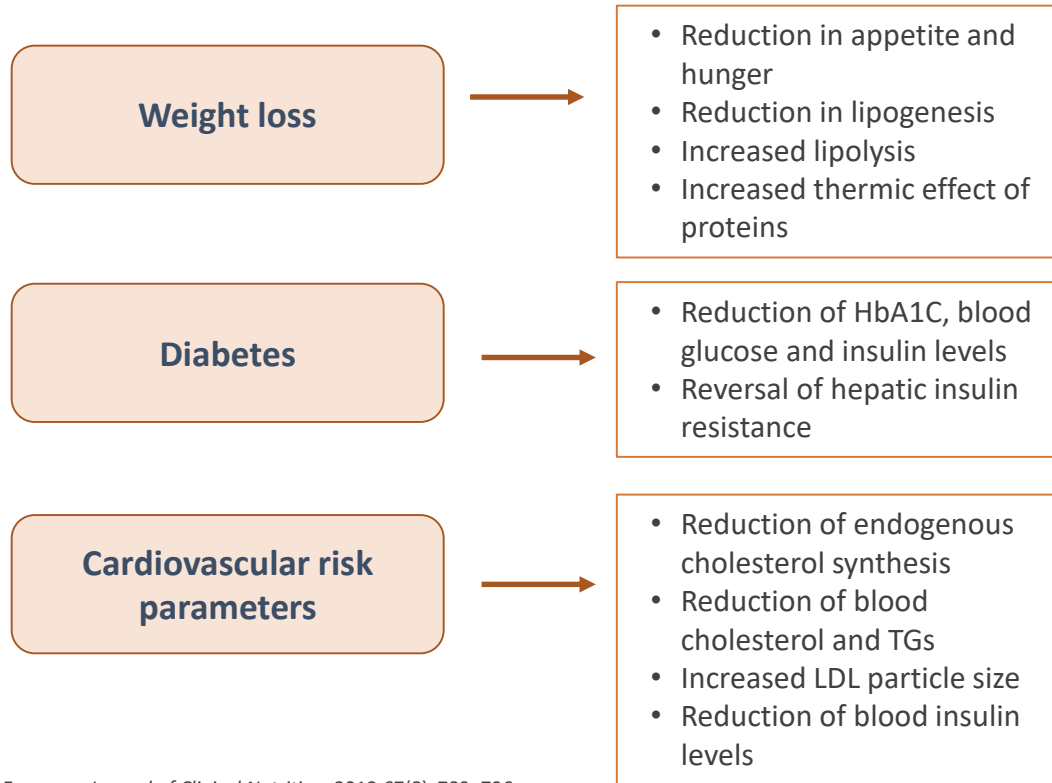
Standard American diet (SAD) — no exercise

SAD 3-5 days per week of exercise (30 min)

## Results

The change over time from week 0 to week 10 was significant in the ketogenic group for **weight, body fat percentage, BMI, HbA1c and ketones**

# How ketogenic diets regulate obesity and its associated pathologies?

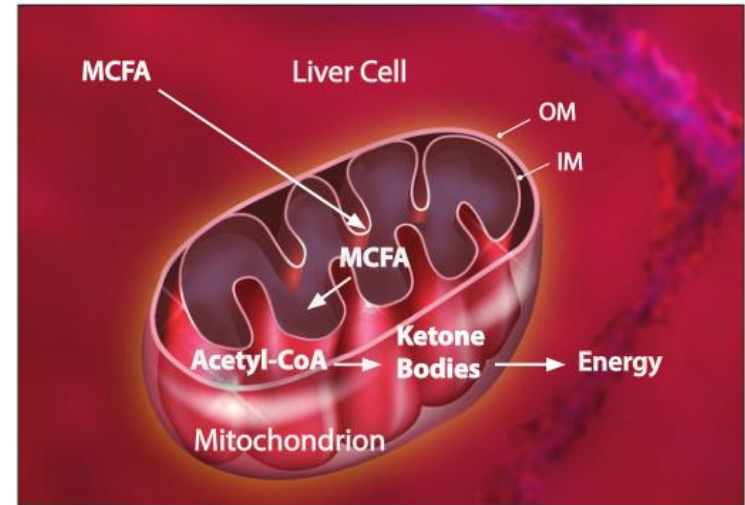


Adapted from: Paoli A et al. *European Journal of Clinical Nutrition*, 2013;67(8): 789–796

# Choosing the right fat for ketogenic programs

## How do medium chain triglycerides (MCT) increase ketone bodies?

- The MCTs contain 6 to 12 carbon atoms, including caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), and lauric acid (C12:0)
- In the liver, MCFA can freely cross the inner mitochondrial membrane (compared with other types of fatty acids who can enter in a more regulated manner)
- This more rapid absorption into the inner mitochondrial space transiently increases ketone body formation<sup>1</sup>



MCFA= medium chain fatty acids, OM = outer membrane, IM = inner membrane

# Effects of MCTs on weight loss, body composition, satiety and cognition:

- A meta-analysis of randomized controlled trials has shown that replacement of long-chain triglycerides (LCT) with MCT (combination of C8:0 and C10:0) in the diet resulted in **greater reduction in body weight and more favorable changes in body composition in both healthy and overweight individuals**<sup>1</sup>
- MCTs supplementation (C8:0 and C10:0) **increased energy expenditure and lipid oxidation compared with LCTs**<sup>2-3</sup>
- In healthy and overweight men, supplementation with MCT **increased satiety at the next meal and reduced food intake compared to LCT**<sup>3-4</sup>
- Ketones derived from MCTs **improved cognition in diabetic and AD patients and attenuate neurodegeneration in mouse models of ALS, MS and AD**<sup>5-7</sup>

1. Mumme K. & Stonehouse W. *Journal of the Academy of Nutrition and Dietetics* 2015; 115:249-263

2. St-Onge M et al. *Obesity Research* 2003; 11(3):395-402

3. Van Wymelbeke V et al. *The American Journal of Clinical Nutrition* 2001; 74:620-30

4. St-Onge M et al. *European Journal of Clinical Nutrition* 2014; 68(10):1134-40

5. Zhao W et al. *PLoS ONE* 2012; 7(11):e49191

6. Kim DY et al. *PLoS ONE* 2012; 7(5):e35476

7. Henderson S et al. *Nutrition & Metabolism* 2009; 6:31

# Majority of human clinical studies have been performed with the mixture of C8+C10

Outcomes	C8	C10	C8+C10
<b>Increased circulating ketones</b>	Henderson S et al. <i>Nutrition &amp; Metabolism</i> 2009; 6:31 Vandenbergh C et al. <i>Current Developments in Nutrition</i> 2017; 1:1-5	Vandenbergh C et al. , <i>Current Developments in Nutrition</i> , 2017; 1:1-5	Courchesne-Loyer A et al. <i>Nutrition</i> 2013; 29:635-40 Ota M et al. <i>Psychopharmacology</i> 2016; 233(21-22):3797-3802 Tsuji H et al. <i>Journal of Nutrition</i> 2001; 131(11):2853-9 Vandenbergh C et al. <i>Current Developments in Nutrition</i> 2017; 1:1-5
<b>Improved weight loss and body composition, increased satiety</b>	St-Onge M et al. <i>European Journal of Clinical Nutrition</i> 2014; 68(10):1134-40		Mumme K. & Stonehouse W. <i>Journal of the Academy of Nutrition and Dietetics</i> 2015; 115:249-263 St-Onge M et al. <i>Obesity Research</i> 2003; 11(3):395-402 Tsuji H et al. <i>Journal of Nutrition</i> 2001; 131(11):2853-9 Van Wymelbeke V et al. <i>American Journal of Clinical Nutrition</i> 2001; 74:620-30 Krotkiewski M <i>International Journal of Obesity</i> 2001; 25:1393-1400
<b>Enhanced cognitive performance</b>	Henderson S et al. <i>Nutrition &amp; Metabolism</i> 2009; 6:31 Henderson S et al. <i>BMC Medical Genetics</i> 2011; 12:137		Page KA et al. <i>Diabetes</i> 2009; 58:1237-1244 Ota M et al. <i>Psychopharmacology</i> 2016; 233(21-22):3797-3802

Additional actions including activation of PPAR $\gamma$  and improvements in mitochondrial efficiency have been demonstrated with both C8 and C10 (Liberato MV et al. *PLoS ONE* 2012; 7(5):e36297; Malapaka RRV et al. *J Biol Chem* 2012; 287(1): 183-95)



# Emerging science—separating fact from fiction

Headlines	Study findings	References
KD increases longevity	Preclinical studies on male mice show that KD <i>reduced midlife mortality</i>	Newman JC et al. <i>Cell Metabolism</i> 2017; 26:547-57 Roberts MN et al. <i>Cell Metabolism</i> 2017; 26:539-46
KD induces mental clarity	Preclinical studies on male rodents show that KD <i>improves learning and memory outcomes in models of neurodegenerative diseases</i>	Kashiwaya Y et al. <i>Neurobiology of Aging</i> 2012; 1-10 Reger M et al. <i>Neurobiology of Aging</i> 2004; 25:311-14 Kim DY et al. <i>PLoS ONE</i> 2012; 7(5):e35476 Zhao W et al. <i>PLoS ONE</i> 2012; 7(11):49191
KD improves cognition	KD research has historically focused on <i>neurological disorders</i> whereas cognitive outcomes in healthy subjects have been <i>anecdotally reported</i>	Kashiwaya Y et al. <i>Neurobiology of Aging</i> 2012; 1-10 Reger M et al. <i>Neurobiology of Aging</i> 2004; 25:311-14 Kim DY et al. <i>PLoS ONE</i> , 2012; 7(5):e35476 Zhao W et al. <i>PLoS ONE</i> 2012; 7(11):49191
KD and mood	Preclinical studies have shown <i>anxiolytic effects</i> associated with KD whereas few case reports have been published showing benefits in humans	Ari C et al. <i>Frontiers in Molecular Neuroscience</i> 2016; 9:137 El-Mallakh RS & Paskitti ME <i>Medical Hypothesis</i> 2001; 57(6):724-26 Bostock ECS et al. <i>Frontiers in Psychology</i> 2017; 8:43

# Emerging science—novel research areas

## Healthy aging

- Longevity
- Reduce age-associated morbidity

## Cognition

- Augmentation
- Prevention of decline
- Biohacking

## Stress

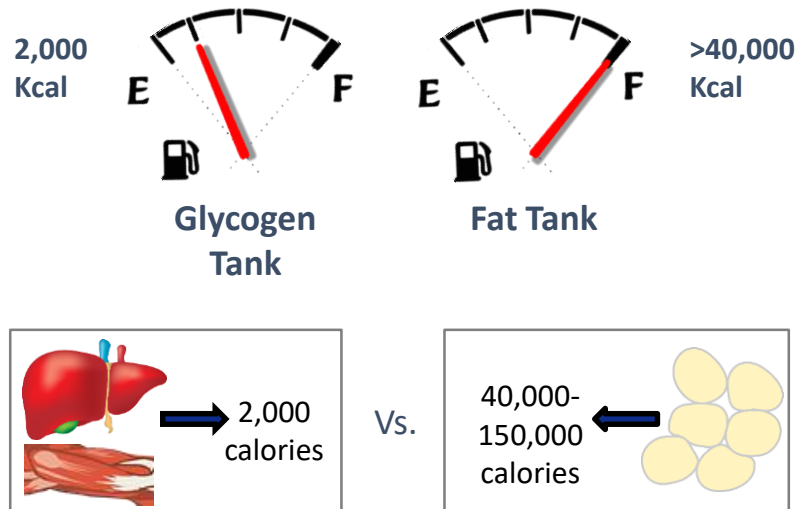
- Resilience
- Prevention

## Microbiome

- Gut-brain axis
- Increased diversity

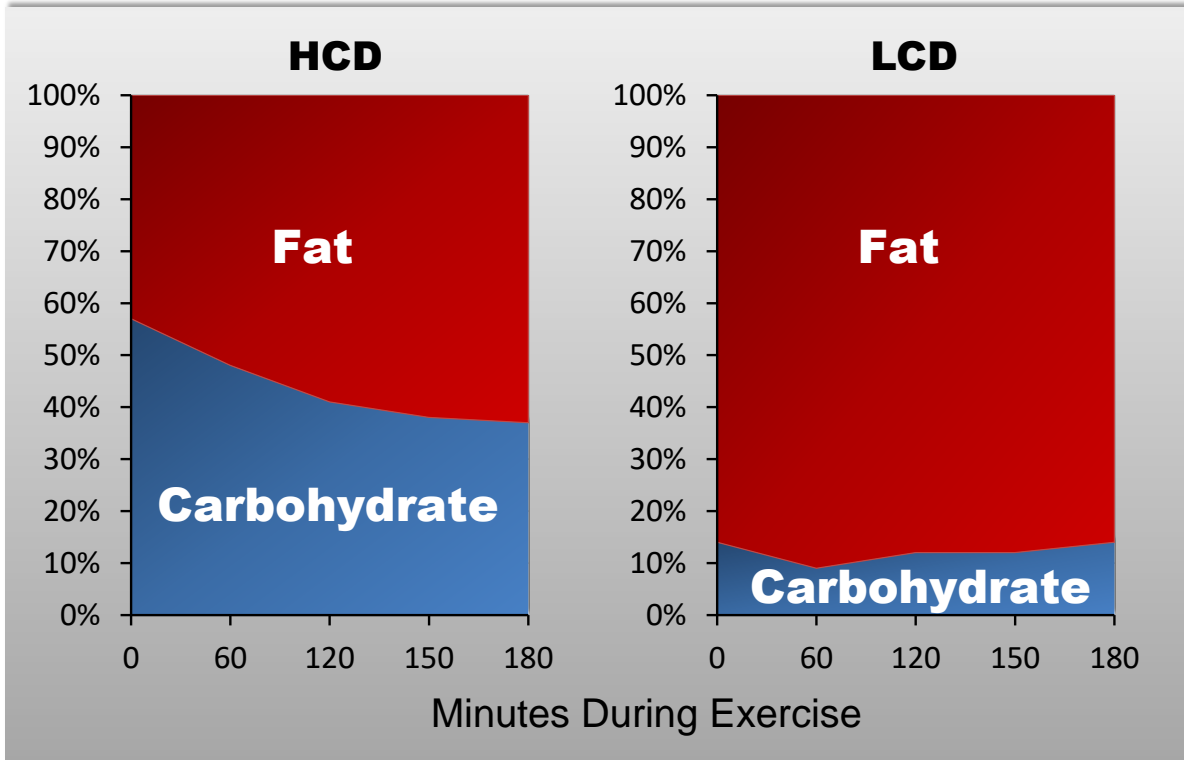
# Ketogenic diet's impact on: Athletic performance

# Which fuel tank do you want access to?



- **Limited energy stored as glycogen** (liver and muscle)
- Fat deposits provide large energy stores
- High carbohydrate diets can reduce the metabolic flexibility needed to utilize fat deposits following glycogen depletion
- **Keto-adaptation promotes access to fat deposits as fuel source**

# Fuel use during submaximal exercise



# Health

- Low carbohydrate diets are anti-inflammatory
- Produces less oxidative stress during exercise
- More rapid recovery between exercise sessions
- Much less dependence on muscle glycogen
- Less need to reload with carbohydrates during and after exercise
- Low carb adaptations accelerates the use of saturated fats of fuel, allowing a high intake of total fats (including saturated) without risk
- By reducing oxidative stress and inflammation, gut and immune functions are better maintained

Adapted from The Art and Science of Low Carbohydrate Performance by Jeff S Volek and Stephen D. Phinney

# Exercise

- Protein-Sparing: When keto-adapted, the body improves its efficiency of protein utilization
- BOHB ketones associated with better maintenance and increase in BCAA# which are essential proteins (ketones can be burned in place of BCAA)
- Less central fatigue when keto-adapted
- Less accumulation of lactate when keto-adapted
- Besides fuel, ketones provide substrates to help repair damaged neurons
- Ketones are like a clean-burning fuel: decrease ROS production, increase antioxidant defenses

Adapted from *The Art and Science of Low Carbohydrate Performance* by Jeff S Volek and Stephen D. Phinney

# Benefits of ketosis for athletes

- Preservation of glycogen stores from ketogenic diet (KD) prevent endurance athletes from “hitting the wall” while performing endurance exercises
- Keto-adaptation can lead to less reliance on carbs during endurance exercise—can help athletes during events with limited access to food or those who can’t easily digest carbs during exercise
- Diet promoting more fat loss important to improve ratio of fat to muscle—crucial for those looking to improve exercise performance or meet certain weight goals for their sport
- Exercising while glycogen stores are low is training technique popular for improving mitochondria function
- Eating KD might also be good diet practice for athletes off-season as they maintain their health while resting

Volek JS, Noakes T, Phinney SD. *Eur J Sport Sci.* 2015;15(1):13-20

Paoli A, Bianco A, Grimaldi KA. *Exerc Sport Sci Rev.* 2015 Jul;43(3):153-62



# FASTER Study

## *Fat Aadapted 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)



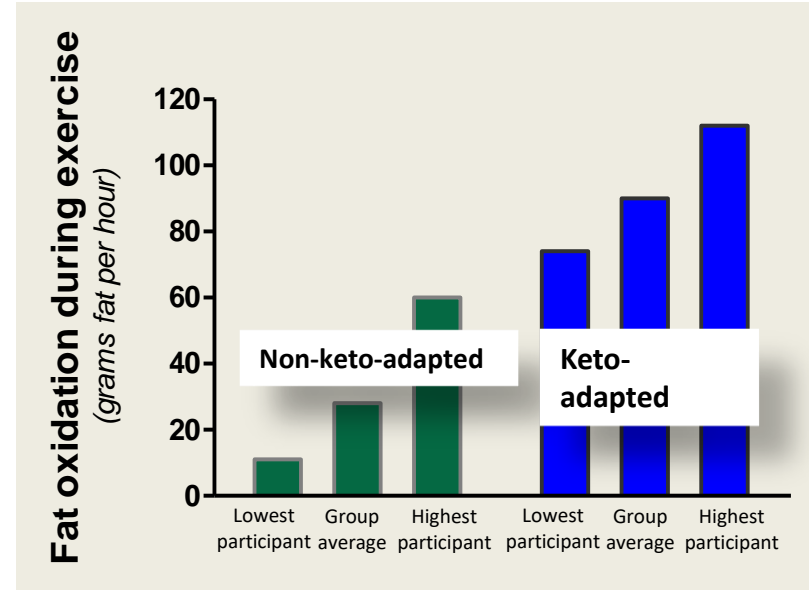
## Metabolic characteristics of keto-adapted ultra-endurance runners



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

# Keto-adaptation enhances endurance performance and body composition in athletes

- Keto-adaptation **improves endurance capacity** and **improves fat mobilization and oxidation** during exercise performance<sup>1,2</sup>
- Liver and muscle **glycogen deposits are maintained**, attenuating glycogen depletion observed in athletes consuming high-carbohydrate diets<sup>1</sup>
- Keto-adaptation **improved aerobic and anaerobic exercise capacity**, as well as **body composition** in endurance athletes<sup>2</sup>



Adapted from: Volek et al. *European Journal of Sport Science* 2015; 15(1):13-20

1. Volek S et al. *European Journal of Sport Science* 2015; 15(1): 13-20

2. McSwiney FT et al. *Metabolism* 2018; 81:25-34

# Nutritional supplements to support ketosis

- **Turmeric:** results in blood glucose stabilization and lowered triglyceride levels

Neerati P, Devde R, Gangi AK. *Phytother Res.* 2014;28:1796–1800.

- **Chromium:** increases production and release of glucose transport molecule
  - Glut-4 enzymes in liver and muscle tissue



Qiao W, Peng Z, et al. *Biol Trace Elem Res.* 2009 Nov;131(2):133-42.

# Nutritional supplements to support ketosis (cont'd)

- Acetyl-L-carnitine: critical for fat metabolism and energy production in the cellular mitochondria
- ALA: unique and powerful antioxidant that has both water and fat soluble properties
- Omega-3 (fatty fish): One of the best foods to eat to stay in ketosis:
  - Ensures omega-3 to omega-6 ratio
  - Natural anti-inflammatory
  - Contributes to keto diet high-fat intake requirement

# Nutritional supplements to support ketosis

- With growing popularity of low-carbohydrate and ketogenic diets, interest has increased in exploring additional nutritional strategies and solutions to facilitate:
  - Achieving or sustaining ketosis
  - Keto-adaptation process
  - Convenience to ensure long-term adherence to ketogenic program
- Examples considered:
  - Exogenous Ketones ( $\beta$ HB)
  - Medium Chain Triglycerides (MCT)

# Nutritional supplements to support ketosis

## Exogenous ketone ( $\beta$ HB) salt

- Exogenous ketone supplementation **induces acute ketosis**
- Anecdotally, keto salts have been **associated with a reduction of the adverse events observed in patients**, and therefore, can facilitate adherence to ketogenic diet
- In animal models, acute and chronic oral  $\beta$ HB salts:
  - Increase plasma ketone levels
  - *Average ketone levels correlated positively with HDL-C and negatively with blood glucose levels, adipocyte volume and serum lipolysis products<sup>1-2</sup>*
- Combination of  $\beta$ HB salt + MCT:
  - In rodents, combining  $\beta$ HB salt and MCT sustained ketosis for longer periods than  $\beta$ HB administration alone<sup>1</sup>

1. Kesl et al. *Nutrition & Metabolism* 2016;13:9,

2. Caminhotto RO et al. *Nutrition & Metabolism* 2017; 14:31

# Nutritional supplements to support ketosis

Very limited human intake data for  $\beta$ HB salt <sup>1</sup>

## Rationale and objectives of Functional Medicine Research Center (FMRC) study\*

### Study Objectives

#### ***Primary objective***

To characterize the change in circulating ketone bodies over a 4-hour period after consumption of varying doses of  $\beta$ HB, compared with placebo control.

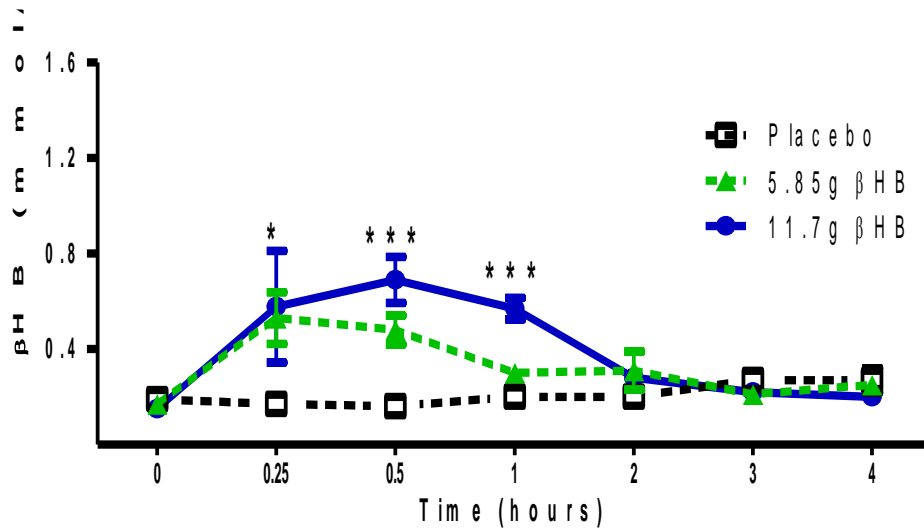
#### ***Secondary objective***

To assess tolerance and adverse events in response to acute intake of each formulation.

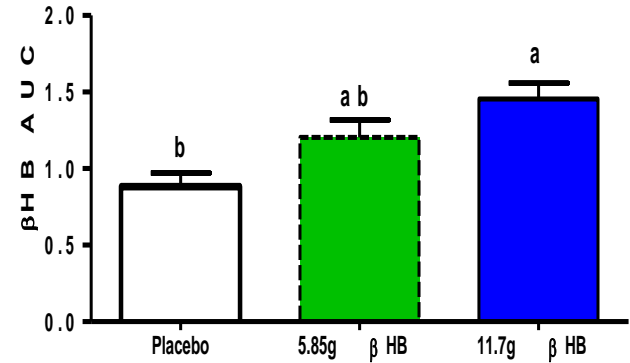
1. Stubbs BJ et al. *Frontiers in Physiology* 2017; 8:848

\* Data on file. *Manuscript in development*

# Acute intake of $\beta$ HB salt increases circulating $\beta$ HB concentrations within 15 minutes\*



Differences between groups assessed with Friedman test. \*'s denote significant ( $p < 0.05$ ) main effect indicated



Data displayed as mean  $\pm$  SEM. Differences between groups assessed with Friedman test, with Dunnett's test. Between-treatment differences denoted as <sup>a,b</sup> with treatments not sharing a letter considered significantly different ( $p < 0.05$ ).

## Additional considerations

- **No changes in blood glucose levels** were observed following acute intake of  $\beta$ HB salt
- **Adverse events:** only one subject reported mild AE (loose stool) following intake of dose 1



# Summary\*

- Consumption of 11.7g of  $\beta$ HB led to a significant increase in circulating  $\beta$ HB levels within 1 hour compared to control
- Increases in  $\beta$ HB with a reduced dose (5.85g  $\beta$ HB, PR-763) led to increases in  $\beta$ HB between PR-761 and control (PR-762)
- The magnitude of the rise in  $\beta$ HB was comparable to that seen in physiological ketogenic situations such as ketogenic diet or periods of fasting, and did not approach the range seen with pathological conditions such as diabetic ketoacidosis (DKA)
- Plasma glucose nor blood pressure were adversely affected during the treatment period. Pulse was seen to modestly but significantly decrease with consumption of PR-761

\* Data on file. *Manuscript in development*

# Nutritional supplements to support ketosis (cont'd)

- MCT oil/powder:
  - Body uses this for energy right away
  - Shorter chain length than fatty acids – “quicker” pathway when metabolized
  - Converts to ketones and used for fuel
  - Doesn't store as fat
  - Beneficial on keto diet for energy and staying in fat-burning state



The image shows two tall glasses filled with a thick, chocolate-colored smoothie. The glasses are placed on a white, textured placemat on a dark wooden surface. In the background, there are several almonds scattered on the table, and a small white bowl containing a brown powder, likely the meal replacement mix, is visible. The lighting is soft and natural, highlighting the texture of the smoothie and the ingredients.

## Ketogenic Meal Replacement

- High fat ratio
  - High percentage of C8:C10 MCTs
- Absorbable protein
- Very low carbohydrates
- Vitamins and minerals to support
  - Blood sugar metabolism
  - Fat oxidation

# Keto flu and dehydration

If you are thirsty, you are an hour late and a quart low!

- **2% water loss**

- 50% drop in athletic performance
- Headaches
- Decreased blood pressure
- Loss of appetite

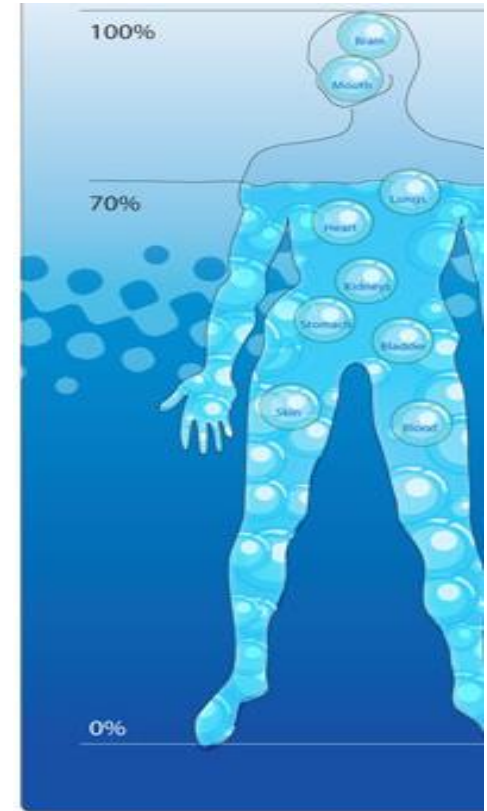
- **5% water loss**

- Paresthesia (numbness)
- Dizziness, fainting or delirium
- Lethargy, sleepiness
- Increased HR and respiration

- **10% to 15% fluid loss**

- Spastic muscles
- Dimmed vision
- Cardiac muscle damage
- Kidney damage
- Seizures

- **15% fluid loss is usually fatal**



## Global study finds low salt diets not beneficial

While our data highlights the importance of reducing high salt intake in people with hypertension, it does not support reducing salt intake to low levels. Our findings are important because they show that lowering sodium is best targeted at those with hypertension who also consume high sodium diets.

— Andrew Mente



## How Much Salt?

4-6 gm

Previous studies have shown that low-sodium, compared to average sodium intake, is related to increased cardiovascular risk and mortality, even though low sodium intake is associated with lower blood pressure.

This new study shows that the risks associated with low-sodium intake — less than three grams per day — are consistent regardless of a patient's hypertension status.

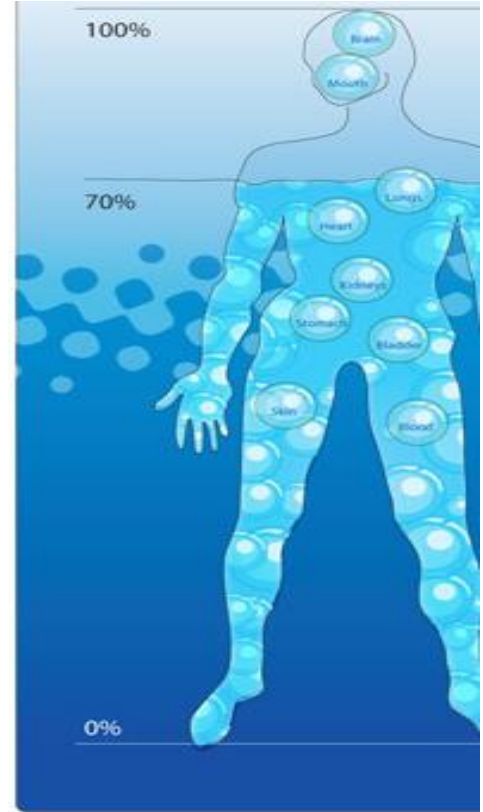
Further, the findings show that while there is a limit below which sodium intake may be unsafe, the harm associated with high sodium consumption appears to be confined to only those with hypertension.

Only about 10 per cent of the population in the global study had both hypertension and high sodium consumption (greater than 6 grams per day).

# Minimum daily hydration

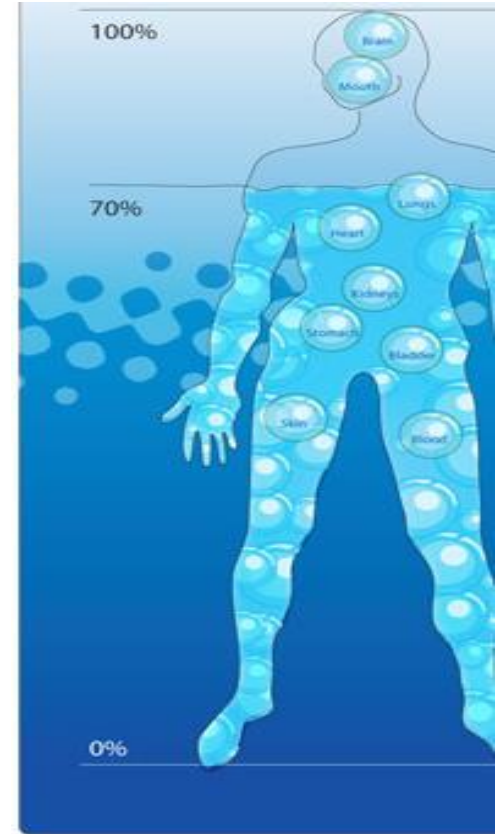
If you are thirsty, you are an hour late and a quart low!

- Daily minimum intake
  - Not including exercise
  - 1/2 oz per lb of body weight
  - 150 lb person needs 75oz per day
- High levels lost in a ketogenic diet
- A sugar craving is often an electrolyte deficiency
- Medications can deplete electrolytes

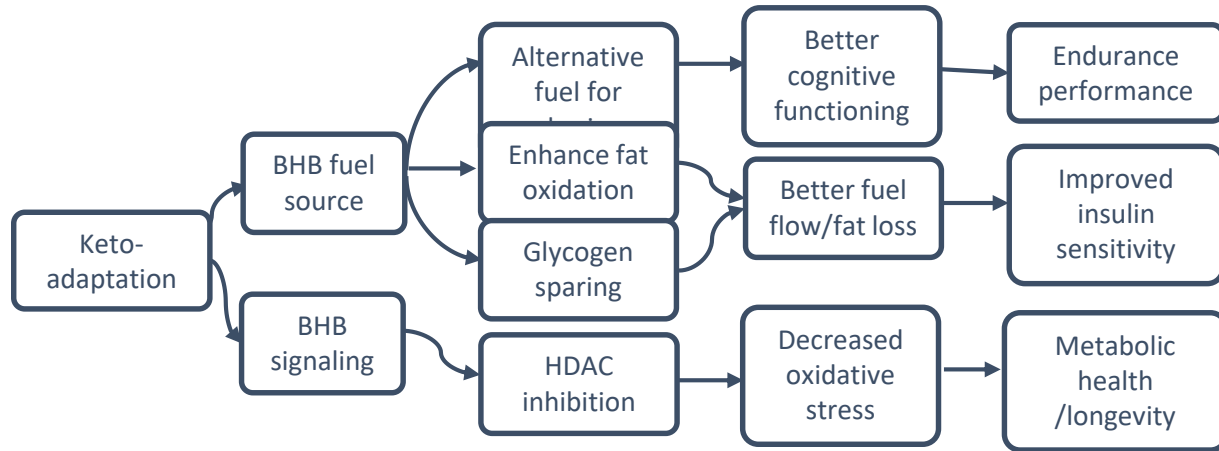


# Sweat rate

- Calculating hydration loss
  - Sweat rates vary 17 – 84 ounces per hour
  - Quick sweat rate calculation:
    - Pre-workout body weight - Post-workout body weight
    - \* Did your weight change? No change, (+), (-)
- Drink 16-24 oz per hour for every pound lost during workout
- 500 – 1000 mg of Na per pound lost
- May take a day or two to recover after a hard workout
- Pale yellow urine good. Dark is bad.



# In summary



Adapted from: Volek et al. *European Journal of Sport Science* 2015; 15(1):13-20

## Ketogenic diets:

- ✓ Increase liver fat oxidation
- ✓ Support weight management
- ✓ Improve insulin sensitivity
- ✓ Reduce hunger and increase both satiety and satiation
- ✓ Likely beneficial for cognition

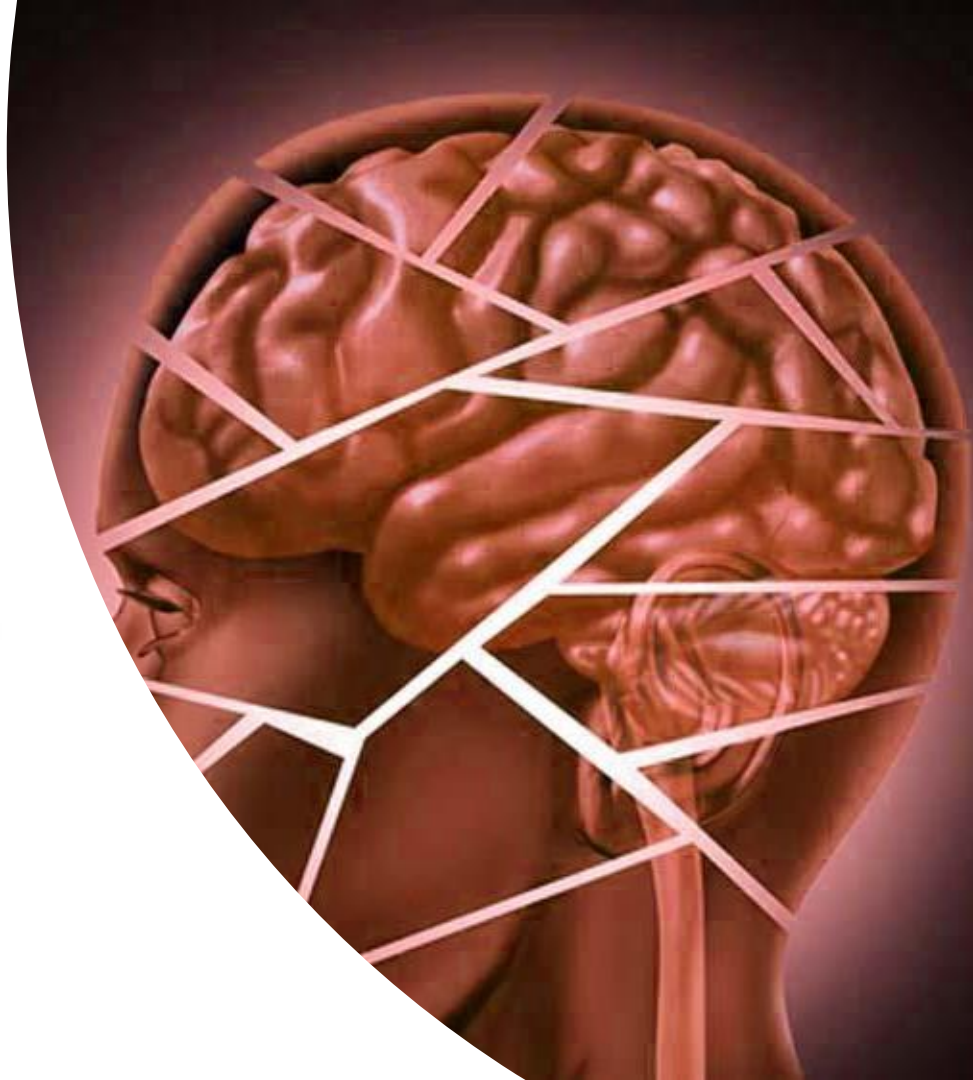
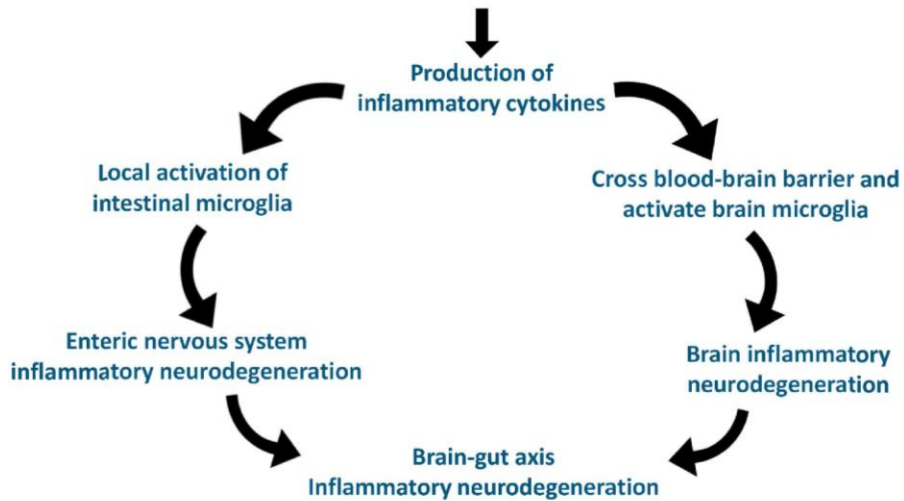
## Ketone bodies:

- ✓ Efficient fuel source
- ✓ Improve mitochondrial bioenergetics
- ✓ Cellular signaling molecule
- ✓ Preserved uptake by the brain



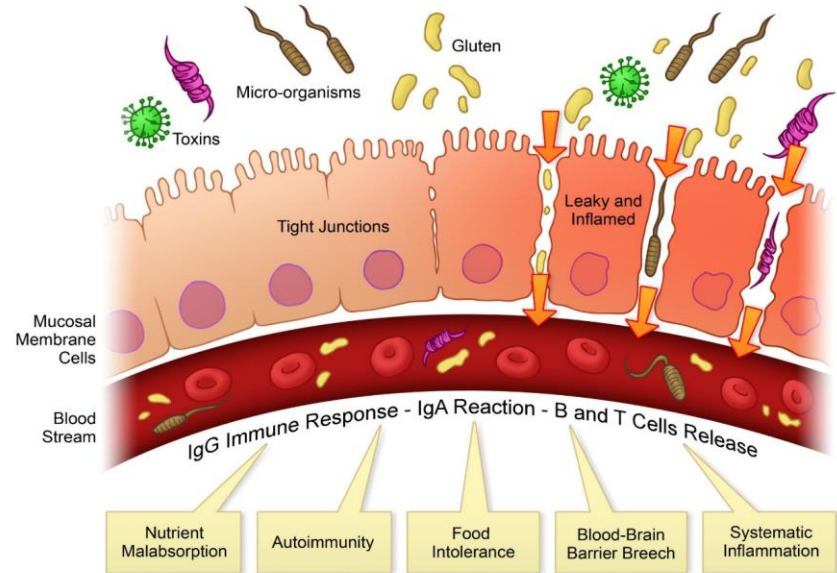
# Gut-Brain connection

## INTESTINAL INFLAMMATION



# Gut to brain

- 400 times the amount of messages from gut to brain than the brain to the rest of the body
- Over 1,000 species of bacteria
- 3 lbs of bacteria in your gut
- Trillions of bacteria in the gut
- 20 million bacteria genes; 2,000 genes in humans
- More bacteria than cells in our body
- Gut contains more neurotransmitters than brain



To treat the brain—must remove cause of inflammation such as leaky gut

# Ketogenic diet's impact on:

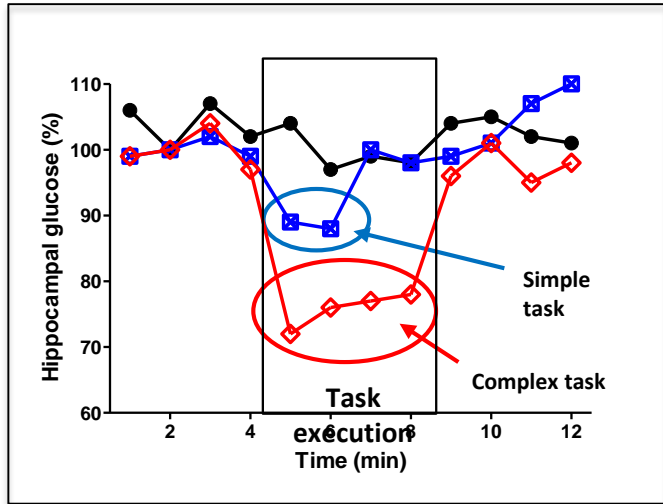
**Fuel for the brain**

**Alzheimer's disease**

**Cognition and aging**

# The human brain is extraordinarily expensive

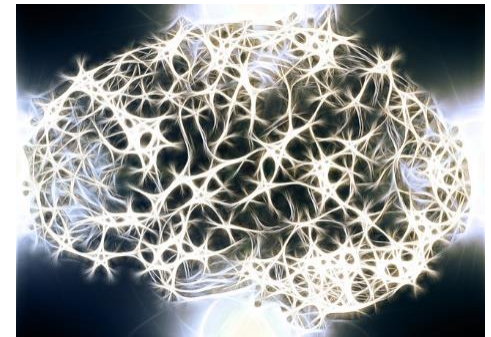
- The human brain comprises 2% of body mass, while requiring approximately 25% daily energy demands (500 kcal)<sup>1</sup>
- **Despite its significant energy requirements, the brain has limited capacity to store glucose**
- The hippocampus is a brain area associated with the execution and retention of learning and memory processes



Adapted from: McNay EC et al. *Proceedings of the National Academy of Sciences* 2000; 97(6): 2881-2885

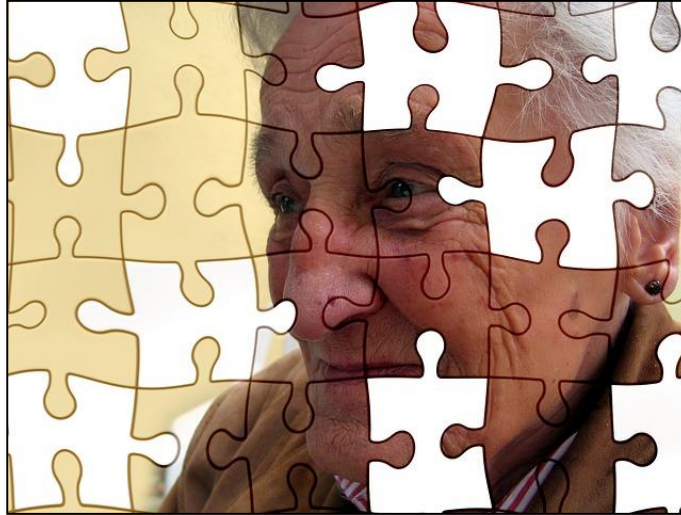
1. Mink JW et al. *American Journal of Physiology* 1981; 241(3): R203-12

- During the execution of cognitively demanding tasks, a decrease in hippocampal glucose levels is observed<sup>2</sup>
- More complex tasks deplete hippocampal glucose levels further
- ***Cognitive performance is limited by fuel availability in the hippocampus***



# Impaired brain glucose utilization and cognitive decline

The healthy young brain relies solely on glucose to obtain energy for its functional and structural needs<sup>1</sup>



During healthy aging, brain **glucose uptake is 10-15% lower and can be up to 35% lower in certain brain areas in neurological disorders** such as Alzheimer's Disease (AD)<sup>1-5</sup>

***This hypometabolism has led researchers to coin the term 'Type 3 Diabetes' when referring to AD***

***Brain uptake of ketones appears to remain normal in the brains of patients with Alzheimer's disease<sup>5</sup>***

1. Hoyer S. *Annals of the New York Academy of Science* 1991; 640:53-8
2. Nugent S et al. *Neurobiology of Aging* 2014; 35:1386-95
3. Mosconi L et al. *Neurobiology of Aging* 2008; 29:676-692
4. Castellano C et al. *Journal of Alzheimer's Disease* 2015; 43(4):1343-53
5. Cunnane S et al. *Frontiers in Molecular Neuroscience* 2016; 9:53

# Can the brain use ketone bodies?



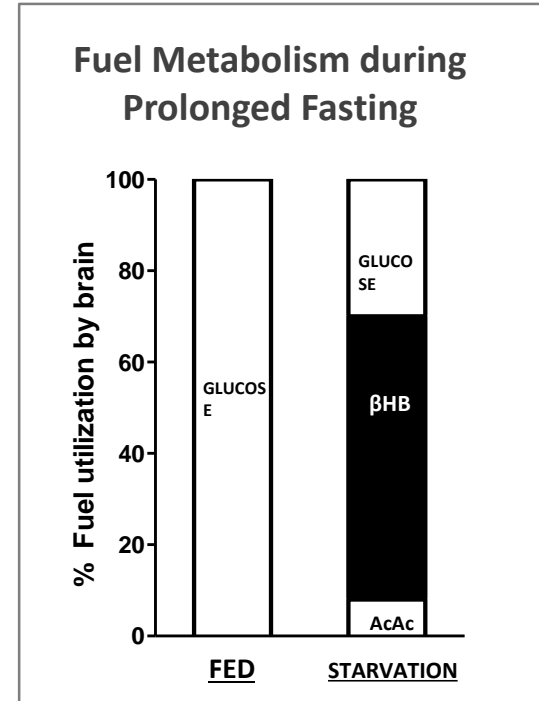
- Common misconception: brain can only use glucose
- Ketone bodies are the only alternative source of energy for the brain (as it cannot utilize FFAs)
- Both rodent and human studies have shown **increased uptake of ketone bodies by the brain**<sup>1,2</sup> following:
  - ✓ Peripheral infusion of ketones
  - ✓ Prolonged fasting
  - ✓ Ketogenic diet

1. Pifferi F et al. *Epilepsia* 2008; 14(2):51-58

2. Cunnane S et al. *Frontiers in Molecular Neuroscience* 2016; 9:53

# Can the brain use ketone bodies?

- When obese subjects underwent prolonged fasting (water access only for 4 to 6 weeks), researchers were able to investigate cerebral energy metabolism during nutrient (glucose) deprivation<sup>3</sup>
- They observed that **up to 70% of brain's energy demands were provided by ketone bodies** available in circulation (blood) and taken up by the brain<sup>3</sup>



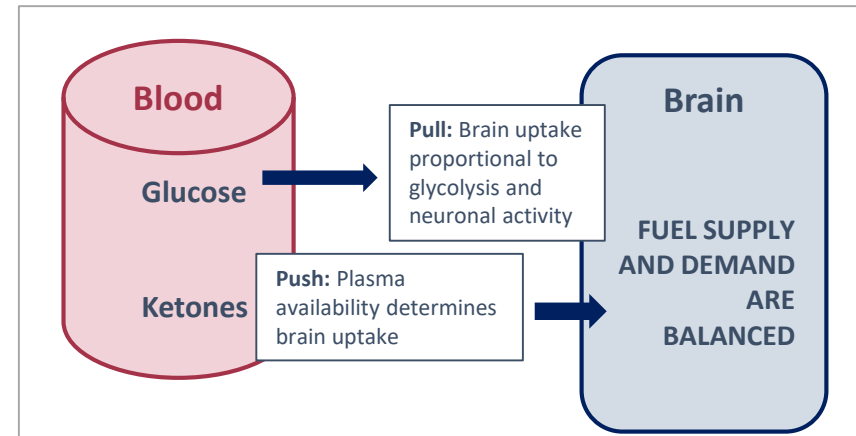
Adapted from: Owen OE et al. *The Journal of Clinical Investigation* 1967; 46(10):1589-95



# Can the brain use ketone bodies?

- Higher circulating levels of ketone bodies result in **higher brain uptake and utilization of ketones** for its energy demands<sup>1</sup>
- **Preserved uptake and utilization of ketone bodies** in the brains of mild cognitively impaired (MCI) patients, whereas glucose uptake and utilization decreases 20-30%<sup>1-5</sup>

## 'Push and Pull' mechanism comparing brain uptake of ketones vs glucose



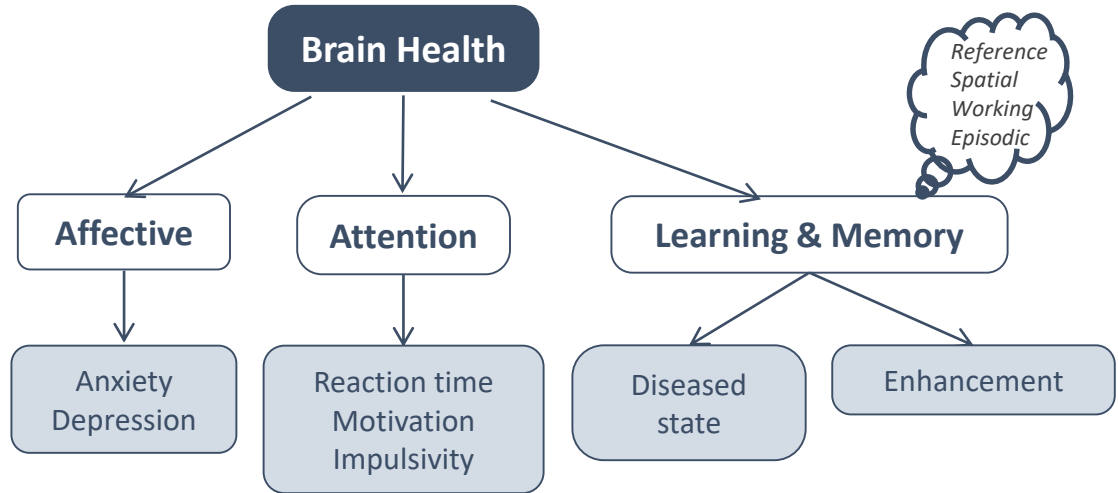
Adapted from: Cunnane S et al. *Frontiers in Molecular Neuroscience* 2016; 9:53

1. Hoyer S. *Annals of the New York Academy of Science* 1991; 640:53-8
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3. Mosconi L et al. *Neurobiology of Aging* 2008; 29:676-692
4. Castellano C et al. *Journal of Alzheimer's Disease* 2015; 43(4):1343-53
5. Cunnane S et al. *Frontiers in Molecular Neuroscience* 2016; 9:53



# Brain health comprises more than memory

- Emerging science suggests that *optimizing cerebral energy metabolism with ketone bodies* may benefit a wide array of neurological conditions<sup>1</sup>
- Research groups have recently started investigating the *potential therapeutic benefits* of ketogenic diets on neurodevelopmental and affective disorders<sup>1,2</sup>
- **Subjective reports and anecdotal evidence suggest a beneficial effect of ketogenic diets on mood<sup>3</sup>, anxiety and attention and further research is needed to validate these claims**



1. Stafstrom CE et al. *Frontiers in Pharmacology* 2012; 3:59  
2. Murphy P et al. *Biological Psychiatry* 2004; 56:981-83  
3. El-Mallakh RS & Paskitti ME *Medical Hypothesis* 2001; 57(6):724-26

# Not all probiotics are created equally

Research is promoting strain-specific probiotics for particular conditions...

...it's not just *Acidophilus*

- The hierarchy of biological classification
- Genus
  - *Lactobacillus*
- Species
  - *acidophilus*
- Strain
  - *Lactobacillus acidophilus* NCFM
  - *Bifidobacterium lactis* Bi-07



You might not choose this particular dog to guard your home

**The P's and O's of Probiotics: A Consumer Guide for Making Smart Choices**  
Developed by the International Scientific Association for Probiotics and Prebiotics (ISAPP) [www.isapp.eu/](http://www.isapp.eu/)

The concept of probiotics has been around for over 100 years, but scientists are just starting to understand their role in maintaining health, regulating the immune system and managing disease. There are hundreds of probiotic products available and an overwhelming amount of information for consumers to sort through. The International Scientific Association for Probiotics and Prebiotics (ISAPP) has developed the following key criteria to help consumers find a credible probiotic product.

**PROBIOTIC STRAIN: Not all probiotics are created equal**

- Different strains of even the same species can be different. Probiotics within the same genus (or group) such as *Bifidobacterium*, do not necessarily provide the same benefits. A probiotic is defined by its genus (e.g. *Lactobacillus*), species (e.g. *acidophilus*) and strain designation (often a combination of letters or numbers). The same strain is complicated, but they are important to connecting the specific probiotic strain to the strain's published scientific literature.
- Look for clear "Other" product manufacturers will create a trademark ("1" or registered trademark (®) name for the strain product in their products for marketing purposes. It is just an "alias" for the probiotic strain and does not necessarily reflect product quality.

**PROOF: Probiotics must be tested in humans and shown to have health benefits**

- "Clinically proven": Do your homework. Make sure that product claims of health benefits are based on sound research done on the particular probiotic. The product should contain the specific strain(s) of bacteria of the same levels as used in published research. The studies should be performed in humans and published in peer-reviewed journals. Check product labels to see study results. Your pharmacist or healthcare provider should be able to help you sort through the product literature.
- "Clinically proven" does not mean: Some probiotics are used as dietary supplements or ingredients in foods, and cannot legally claim that it can cure, treat or prevent disease. Claims which make the product to health are allowable. Any claim made on a product, no matter how general, is supposed to be truthful and substantiated – but not of manufacturer's own clinical substantiation.
- Did your doctor's OK – Consult a physician before administering probiotics to neonates or newborns or to people with compromised immune systems or other major underlying illnesses. Read "Warnings" and "Other information" on the product package and be aware of any reported symptoms or side effects. Probiotic foods should be safe for the generally healthy population to consume.
- More information – The product you choose should offer resources to find more information, including a Web site or consumer hotline.

**QUALITY AND QUANTITY: Choose a quality product at the right quantity**

- What are CFU – CFU stands for colony forming units, which is the measure of viable microbes in a probiotic. CFU amount should be the same or that shown to be effective in clinical studies. More CFUs does not necessarily mean better quality.
- What is the minimum CFU I should look for? – The important thing to know is that different probiotics have been shown to be effective at different levels. It is not possible to provide one number for all "probiotics" – scientific literature has documented health benefits for products ranging from 100 million to more than 1 trillion CFUs/day.

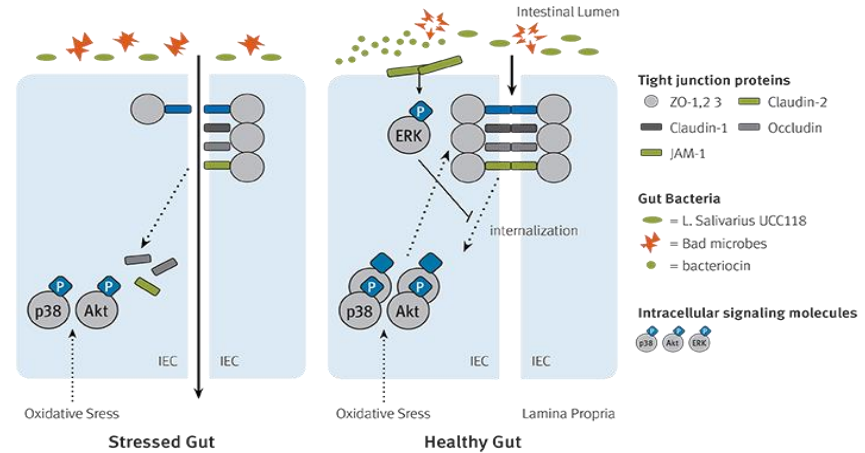
**PACKAGE: Priority quality packaging and a verified manufacturer**

- What are the label tell you? According to the World Health Organization (WHO), probiotic packages should include the following information:
  - Strain – What probiotic is inside?
  - CFU (Colony Forming Units) – How many live microorganisms are in each serving? When does it expire?
  - Suggested serving size – How much do I take?
  - Health benefits – What are the product's key benefits?
  - Storage conditions – When do I keep it to ensure maximum survival of the product?
  - Contains animal-derived substances – Who makes the product? (It is safe for most consumers.)
  - Product is not a probiotic – Health claims of a probiotic – Some products labeled "probiotic" do not have clinically validated strains or levels in the product. Although the scientific definition of probiotic stipulates that products be clinically evaluated, not all manufacturers adhere to it.
  - Fruits or supplements? – Probiotics can be found in various foods, yogurts, and supplements. Probiotic content is generally more uncertain than the age in which you consume them.
  - Live bacteria – Among the end of shelf life – Packaging should ensure an effective level of live bacteria through the "best by" or expiration date. Products should have an expiration date printed clearly on the package. Climate changes, exposure to light and moisture can be important in timing probiotics, etc.
  - Obtain your product from a trusted source – A responsible manufacturer will make sure its probiotic product has the same strain(s) and is as potent through the end of shelf life as what was used in clinical studies.

\*Probiotics are defined by the Food and Agriculture Organization of the United Nations as "live microorganisms, which when administered in adequate amounts confer a health benefit on the host" (<http://www.who.int/nmh/topics/probiotics/en/>)

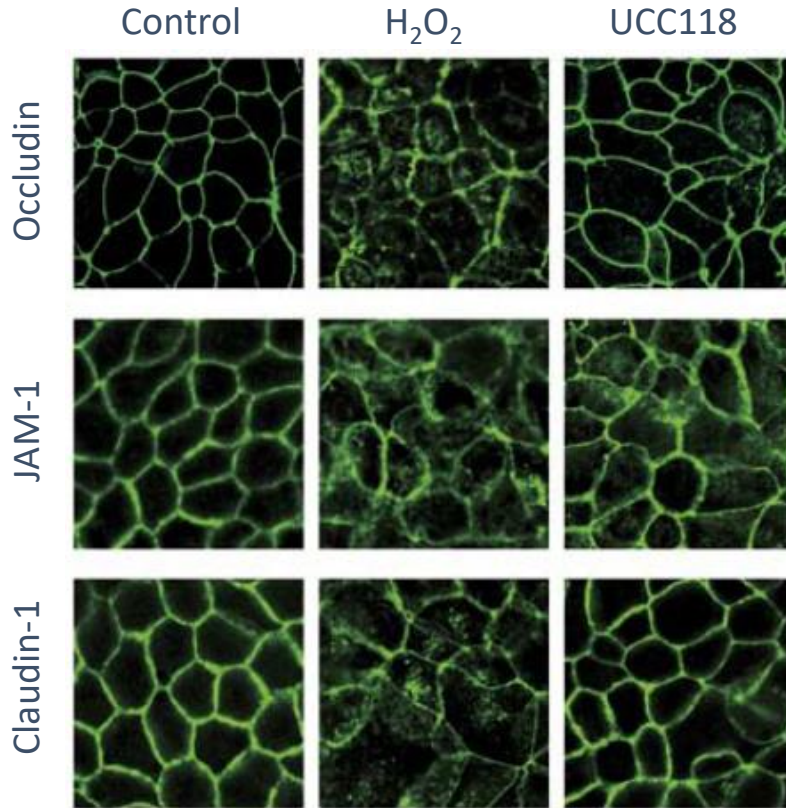
# Effect of *L. salivarius* UCC118 on tight junction proteins

- Study design:
  - Human intestinal epithelial cell line
    - CaCo-2 cells
  - Oxidative stress: hydrogen peroxide ( $H_2O_2$ ) exposure
  - Outcome: localization of tight junction proteins
  - Hypothesis: UCC118 will prevent the cellular internalization of tight junction proteins associated with oxidative stress



Miyauchi et al. *Am J Physiol Gastrointest Liver Physiol.* 2012  
Nov 1;303(9):G1029-41

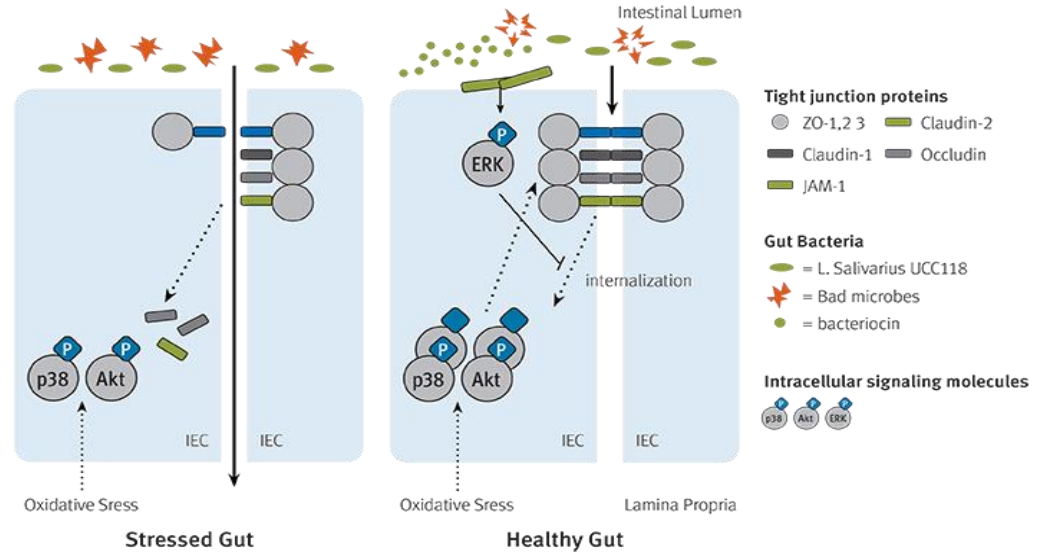
Tight junction proteins



Pretreatment with UCC118 prevents disruption of intestinal epithelial cell tight junctions, in a validated in vitro model of human intestinal epithelial cell oxidative stress

# Conclusions

- *UCC118* prevented the internalization of tight junction proteins after oxidative stress
- Not all strains of *Lactobacillus salivarius* have this capacity
- *UCC118* protects tight junction functionality in intestinal epithelial cells



Miyauchi et al. *Am J Physiol Gastrointest Liver Physiol.* 2012 Nov 1;303(9):G1029-41

## The credibility of health claims for specific probiotic species and strains must be established through science-based clinical studies

### Probiotic genus, species, strain

<i>Lactobacillus salivarius</i> UCC118	Protection against infection by food-borne <i>Listeria</i> ; support of intestinal epithelium integrity by maintenance of tight junctions
<i>Bifidobacterium animalis</i> ssp. <i>lactis</i> 420	Increases SCFA for energy production and weight management
<i>Saccharomyces boulardii</i> , <i>rhamnosus</i> HN001 <i>Bifidobacterium lactis</i> HN019 <i>Lactobacillus</i>	Anti-Viral-Bacterial-Yeast. Prevents pathogen adhesion. Protects sinus and GI mucosal cells
<i>Lactobacillus acidophilus</i> NCFM and <i>Bifidobacterium lactis</i> Bi-07	Reduction of cold and influenza symptoms in children
<i>Lactobacillus plantarum</i> 299V	Support of gut barrier function; improvement of IBS symptoms
<i>Lactobacillus acidophilus</i> NCFM, and <i>L. paracasei</i> Lpc-37, and <i>B. lactis</i> Bi-07, and <i>B. lactis</i> Bi-04	Reduction of antibiotic-associated diarrhea
<i>Lactobacillus reuteri</i> RC-14 and <i>Lactobacillus rhamnosus</i> GR-1	Prevention or treatment of bacterial vaginosis
NCFM, <i>Bifidobacterium lactis</i> Bi-07, Bi-04 <i>Lactobacillus plantarum</i> Lp-115, <i>salivarius</i> Ls-33 <i>Streptococcus thermophilus</i> St-21, <i>S. boulardii</i>	Immune health & digestive support Anti-Viral-Bacterial-Yeast

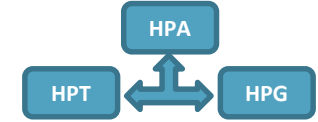
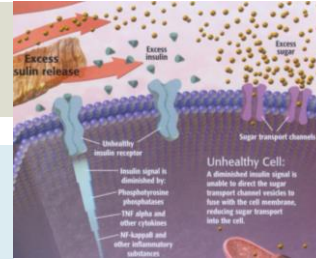
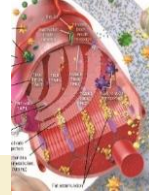
# The 4R Program

Remove

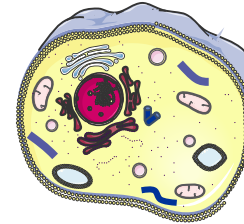
Replace

Reinoculate

Repair



Credit: Lancaster University



## The 4R Program:

### 1. Remove

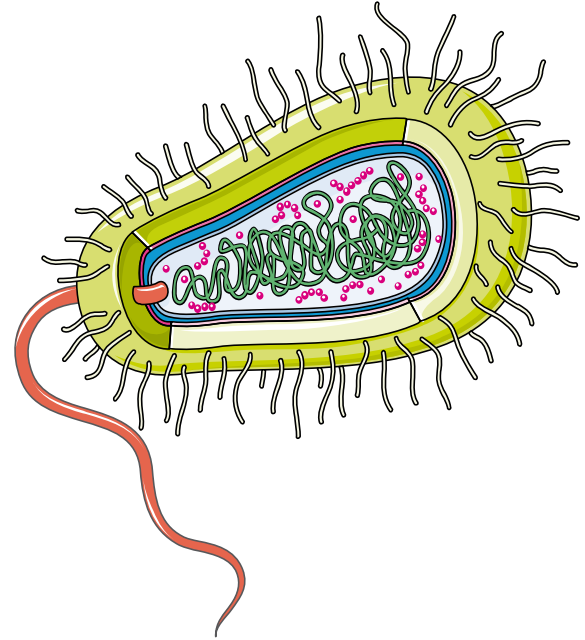
- Removing offending substances from the diet
- Food allergens and other materials that negatively influence the intestinal environment:
  - Can cause localized irritation
  - Triggers release of damaging chemicals into general circulation
  - Affects other tissues or organ



# The 4R Program:

## 1. Remove (cont'd)

- Concentrated aromatic oils:
  - Thyme oil
  - Oregano oil
  - Sage leaf
  - Lemon balm leaf
- For upper respiratory issues/sinusitis
- Aromatic oils – open the bronchial
- Thyme oil – health of GI/upper respiratory
- Sage/lemon balm – herbs that complement and stabilize the fragile essential oils

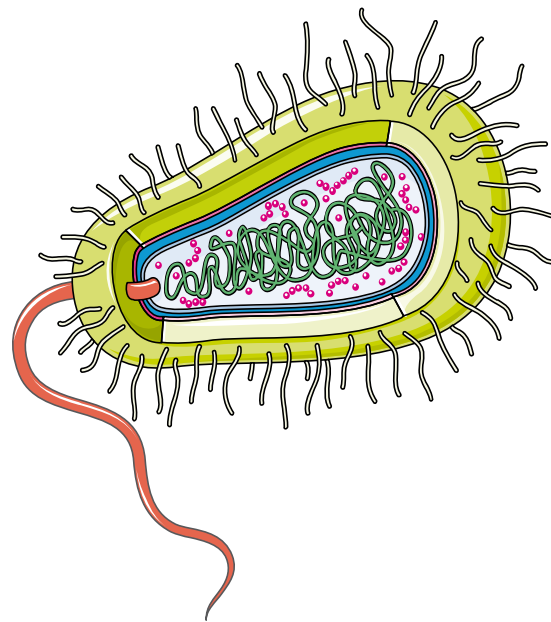


# The 4R Program:

## 1. Remove (cont'd)

### Concentrated berberine formula for intestinal support

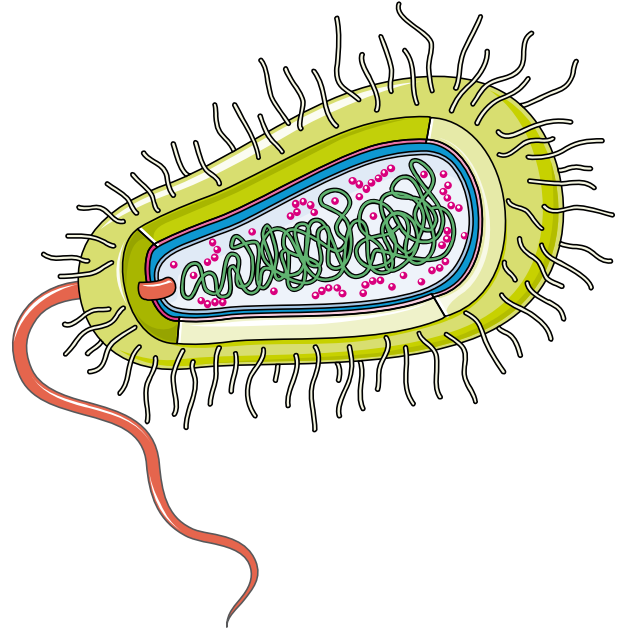
- Berberine HCL
- Oregon grape
  - Coptis root
- Chinese herbs, ginger, licorice, skullcap
- For healthy intestinal environment
- Dyslipidemia, dysbiosis



# The 4R Program:

## 1. Remove (cont'd)

- Enzyme complex to support healthy digestion while breaking down pathogenic biofilm
  - Fungal protease
  - Cellulase
  - Hemicellulase

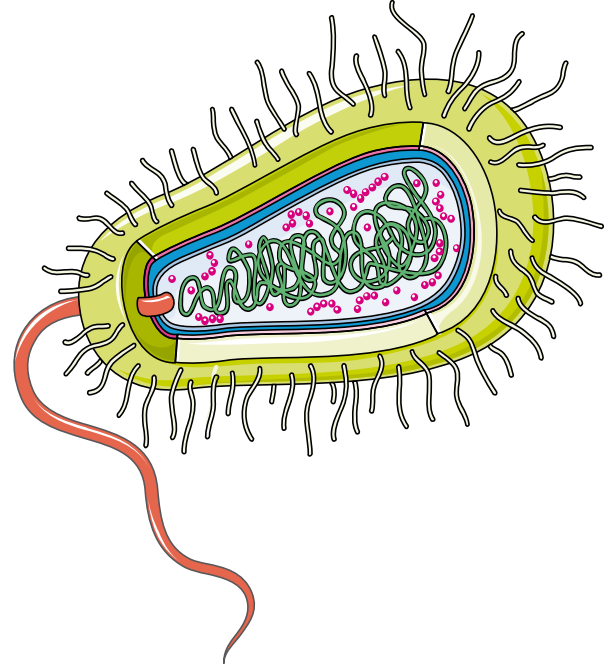


# The 4R Program:

## 1. Remove (cont'd)

### Probiotics to support intestinal health

- *Saccharomyces boulardii*
- *Bifidobacterium lactis* Bi-07
- *Lactobacillus plantarum* Lp-115
- *Lactobacillus salivarius* Ls-33
- *Lactobacillus acidophilus* NCFM
- *Streptococcus thermophilus* St-21
- *Bifidobacterium lactis* BI-04
- *Bifidobacterium lactis* HN019
- *Lactobacillus rhamnosus* HN001



# The 4R Program:

## 2. Replace

### **Low-gastric acidity:**

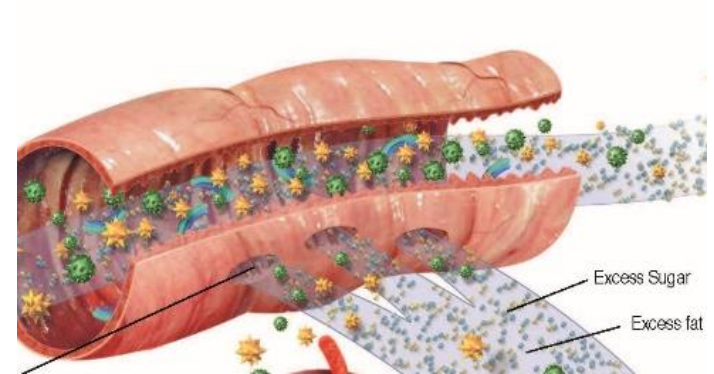
A formulation featuring betaine HCl combined with pepsin to complement the natural production of digestive agents in the stomach

### **Pancreatic enzyme insufficiency:**

An enzyme complex that helps promote healthy digestive function. Containing protease, amylase and lipase

### **Poor lipotropic function:**

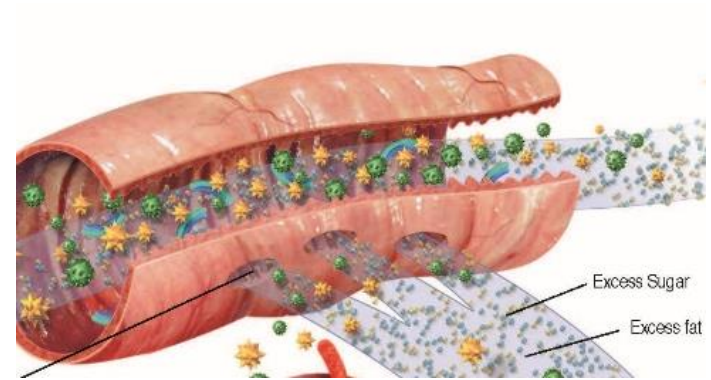
Choline, inositol and taurine to support healthy liver and gallbladder function



## The 4R Program:

### 3. Reinoculate

- *L. acidophilus* NCFM and *B. lactis* Bi-07 (60 billion live organisms)—designed to relieve recurring bowel distress and related functional discomforts, such as occasional bowel urgency
- Helps relieve abdominal discomfort, bloating, cramping, bowel irritation, and occasional urgent bowel movements



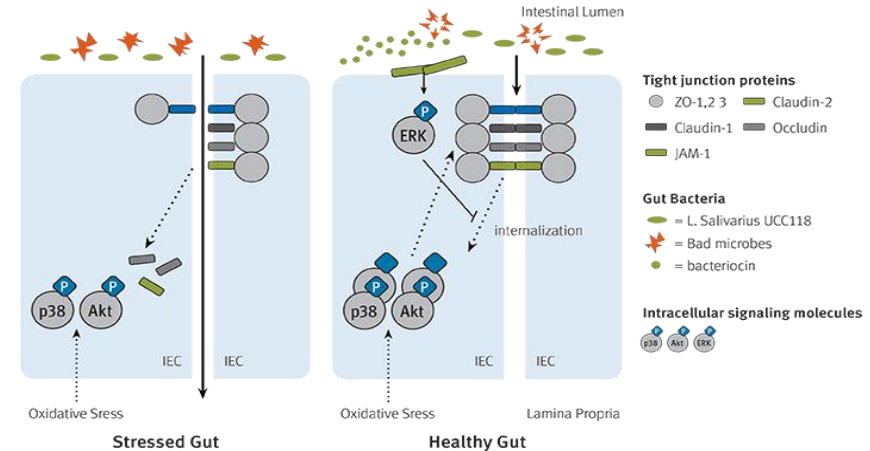


# The 4R Program:

## 4. Regenerate/Repair

### Effect of *L. salivarius* UCC118 on tight junction proteins

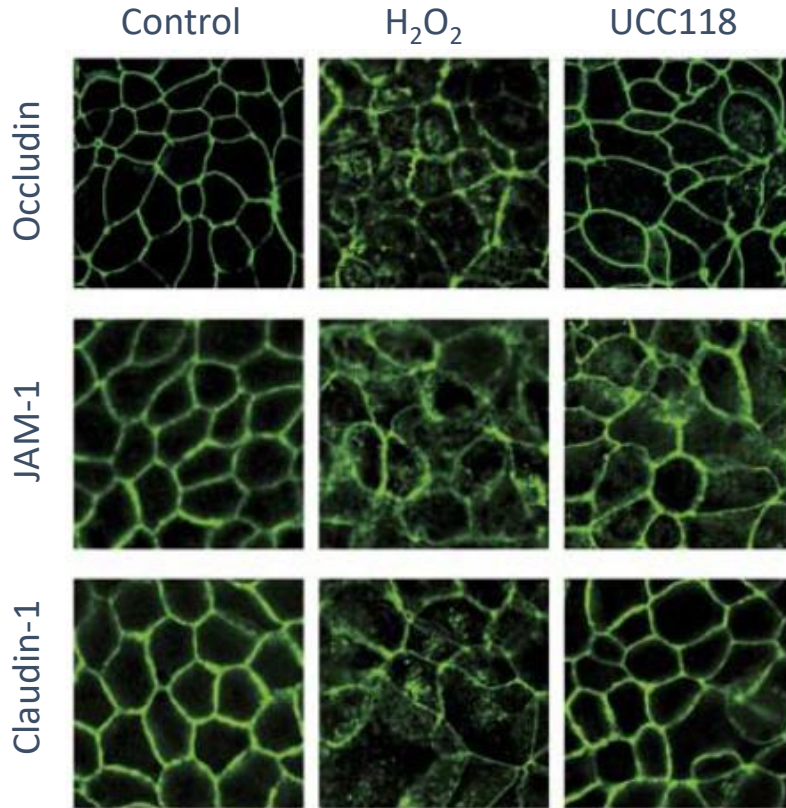
- Study design:
  - Human intestinal epithelial cells:
    - CaCo-2 cells
  - Oxidative stress:
    - Hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) exposure
  - Outcome:
    - Improved tight junction proteins
  - Hypothesis: UCC118 will prevent the cellular internalization of tight junction proteins associated with oxidative stress



Miyauchi et al. *Am J Physiol Gastrointest Liver Physiol*. 2012 Nov 1;303(9):G1029-41



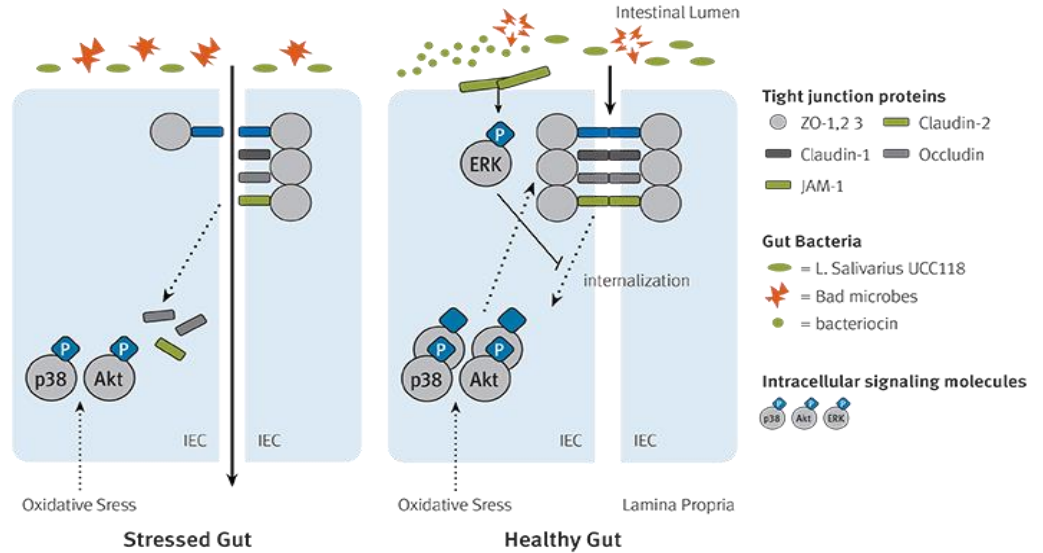
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# Conclusions

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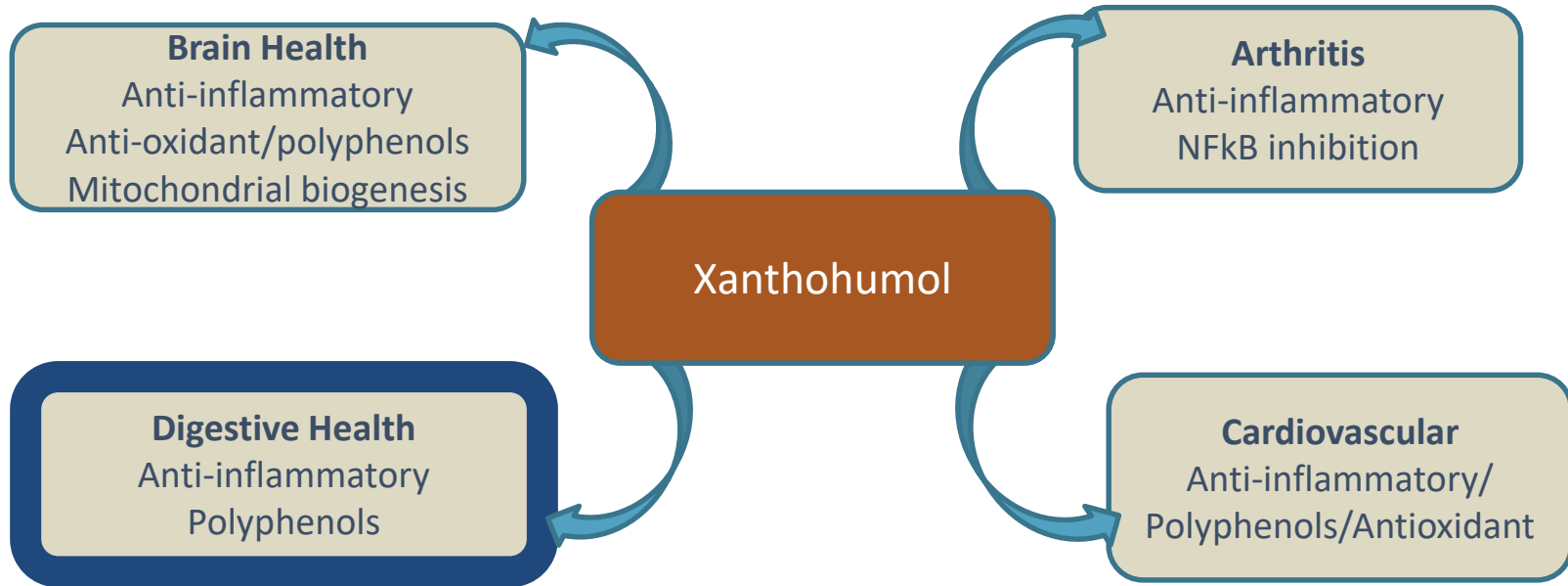


Miyauchi et al. *Am J Physiol Gastrointest Liver Physiol.* 2012 Nov 1;303(9):G1029-41

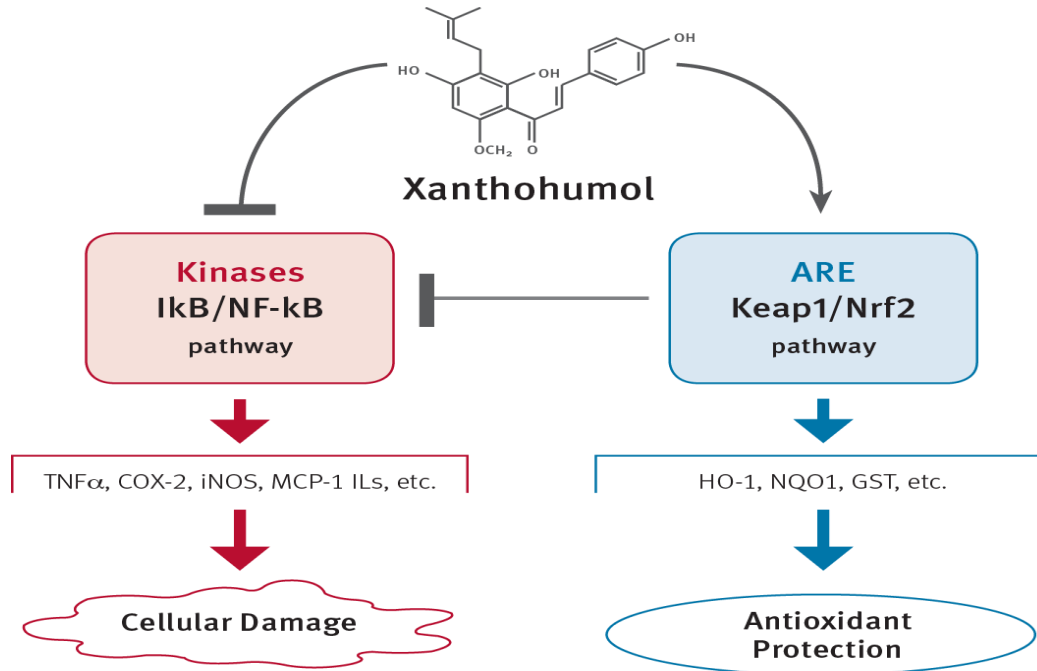
# Xanthohumol: strong clinical data

## Next generation Skrm technology

**Excellent science: >250 publications in preclinical science**



# Xanthohumol modifies kinases in favor of antioxidant protection



# Bioavailable form of curcumin

- Shows potent anti-inflammatory activity—may help reduce inflammation-signaling molecules, such as NF- $\kappa$ B, TNF- $\alpha$ , COX-2, and PGE<sub>2</sub><sup>1</sup>
- Shows potent antioxidant activity – may help improve overall redox status through influencing antioxidants Nrf2, HO-1, and NQO1<sup>2</sup>
- Delivers significant concentrations of biologically active free curcuminoids—regarded as major limitation for efficacy of curcumin supplementation<sup>2</sup>
- Blend of stable curcuminoid and galactomannan compound (from fenugreek) designed for great bioavailability and more reliable clinical outcomes



1. Vecchi Brumatti L, Marcuzzi A, Tricarico PM, Zanin V, Giradelli M, Bianco AM. Curcumin and inflammatory bowel disease: potential and limits of innovative treatments. *Molecules*. 2014;19(12):21127-21153.
2. Rajasekaran SA. Therapeutic potential of curcumin in gastrointestinal diseases. *World J Gastrointestinal Pathophysiology*. 2011;2:1-14. 35. González-Reyes, S. Guzmán-Beltrán S, Medina-Campos ON, Pedraza-Chaverri J. Curcumin pretreatment induces Nrf2 and an antioxidant response and prevents hemin-induced toxicity in primary cultures of cerebellar granule neurons of rats. *Oxid Med Cell Longev*. 2013;2013:801418
3. Krishnakumar IM, Abhilash M, Gopakumar G, Dinesh K, Balu M, Ramadasan K. Improved blood–brain-barrier permeability and tissue distribution following the oral administration of a food-grade formulation of curcumin with fenugreek fibre. *Journal of Functional Foods*. 2015;14:215-225.

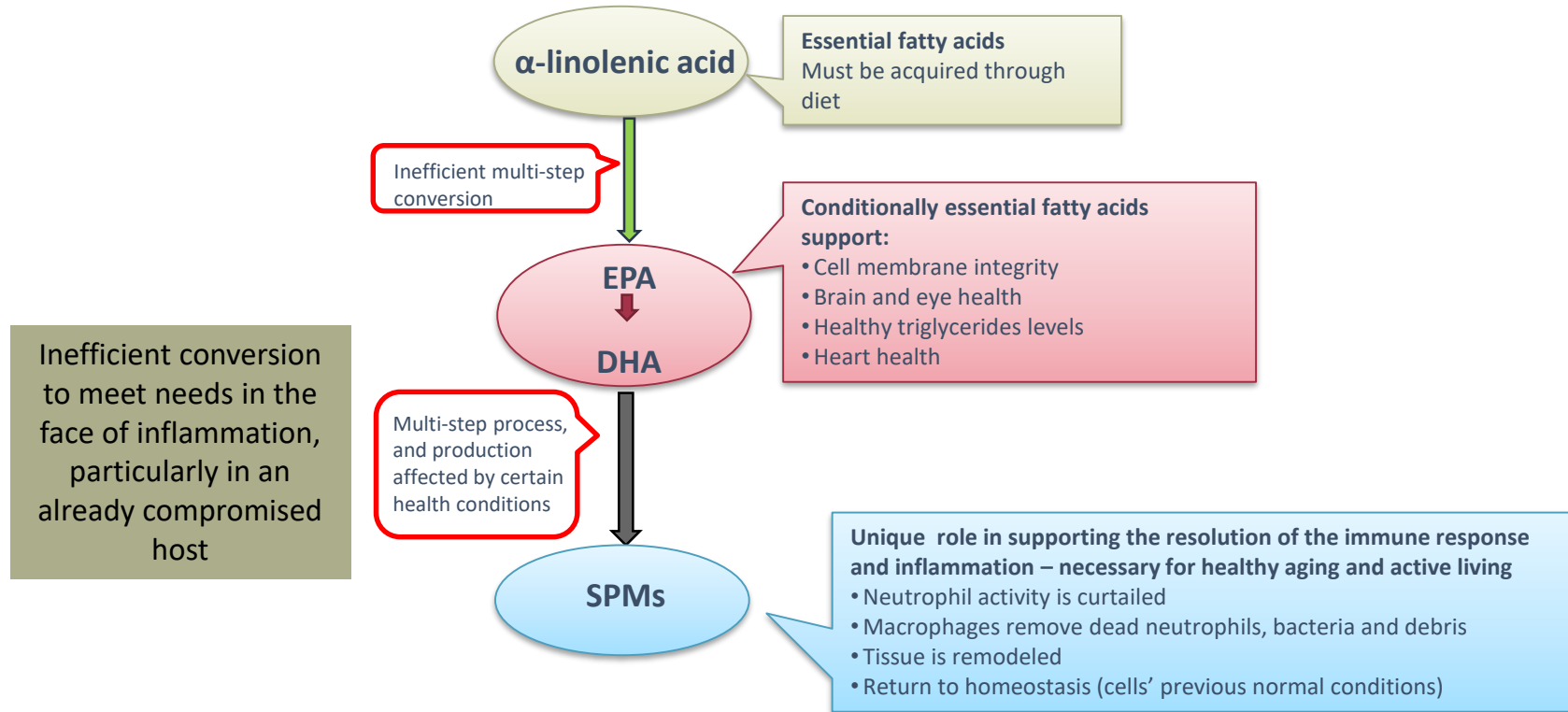
# Isomalto-oligosaccharide (IMO) prebiotic fiber



The average American is only eating 10 - 15g of fiber  
Recommendation for adults is to consume 25 – 35g of fiber

- 4 grams of IMO
- IMO is soluble fiber, gentle prebiotic fiber source from tapioca
- Produced short-chain fatty acid (SCFA) like acetate, propionate and butyrate as end products of fermentation
- Inhibits the growth and activities of harmful micro-organisms and contributes to stimulation of the growth of *Lactobacilli* and *Bifidobacteria*

# Specialized pro-resolving mediators (SPMs)

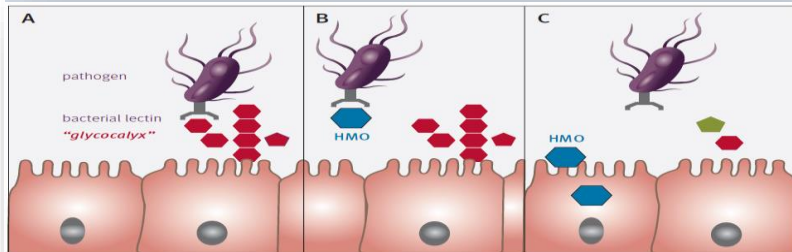


Serhan CN. *Nature*. 2014;510:92-101

# Key targeted ingredients address dysbiosis

- ✓ HMO occur naturally in human milk
- ✓ HMO have prebiotic effect
- ✓ HMOs mimic structures found on surface of intestinal epithelia that bind unwanted bacteria serving as decoy receptors
- ✓ HMOs (2'-FL) selectively promote bacterial growth (*in vitro*) affecting butyrate production

## 2'-FL is the most abundant HMO



- ✓ IMO is soluble fiber, well-tolerated prebiotic fiber source from tapioca
- ✓ Produces [short-chain fatty acid](#) (SCFA) like acetate, propionate and [butyrate](#) as end products of fermentation
- ✓ Inhibits growth and activities of harmful micro-organisms and contributes to stimulation of the growth of [Bifidobacteria](#)



# 4R keto/gut program

## Ingredients

Concentrated aromatic oils, Berberine HCL, Oregon grape, Coptis root, Chinese herbs, Ginger, Licorice, Skullcap

Keto diet, keto meal replacement, MCT oil (10 g/day)

Specialized pro-resolving mediators (1,500 mg/day)

Blend of protease, amylase and lipase

*Strain specific Probiotics per patient's condition*

A low-allergy blend of soluble and insoluble fiber

Xanthohumol, Curcumin, Boswellia, Ginger extracts

# Proactive care

## Ingredients

Keto diet, keto meal replacement, MCT oil (10 g/day)

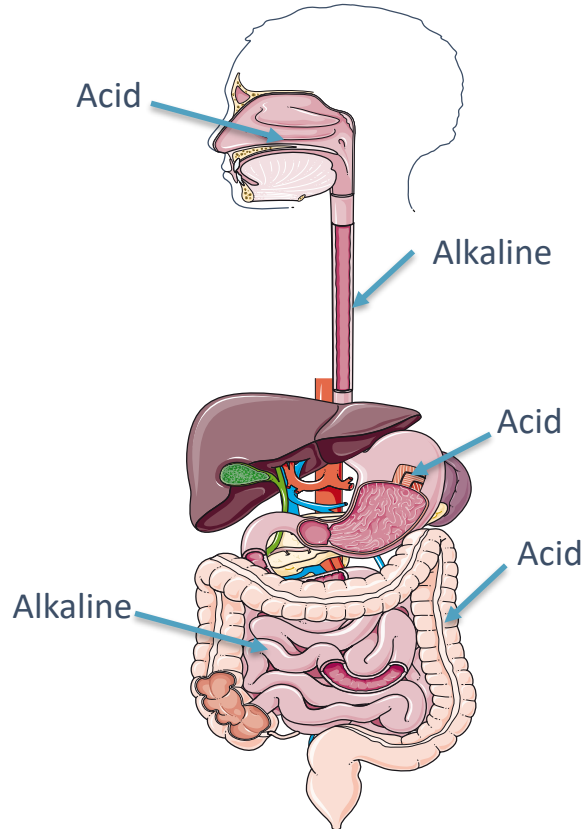
Replenish your gut with IMO/(2'FI), L-alanyl-L-glutamine

Specialized pro-resolving mediators (500 mg/day)

50:50 blend of *L. acidophilus* NCFM & *B. lactis* Bi-07 (15 billion live org total/day)

A low-allergy blend of soluble and insoluble fiber

# SIBO



## Statistics

**IBS** – 15% of adults

- Females – 2:1
- Features:
  - Bloating
  - Cramping
  - Constipation/diarrhea

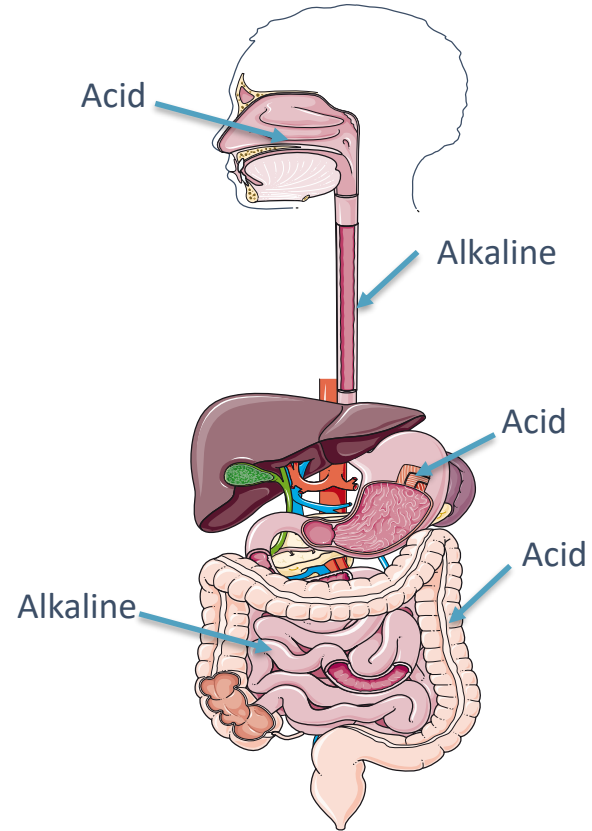
## SIBO

- SI devoid of coliform bacteria
- Is a condition of altered microbiome
- Features:
  - Chronic vitamin malabsorption
  - Constipation

SIBO is a common occurrence of D-IBS

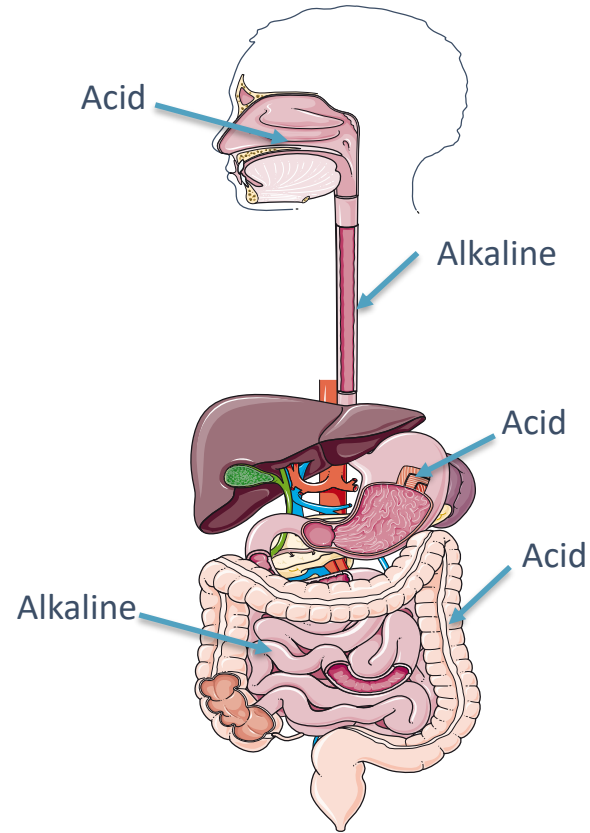
# SIBO symptoms

- Nausea
- Bloating
- Vomiting
- Diarrhea
- Malnutrition
- Weight loss
- Joint pain
- Fatigue
- Rashes
- Acne
- Eczema
- Asthma
- Depression
- Rosacea



# SIBO associated complications

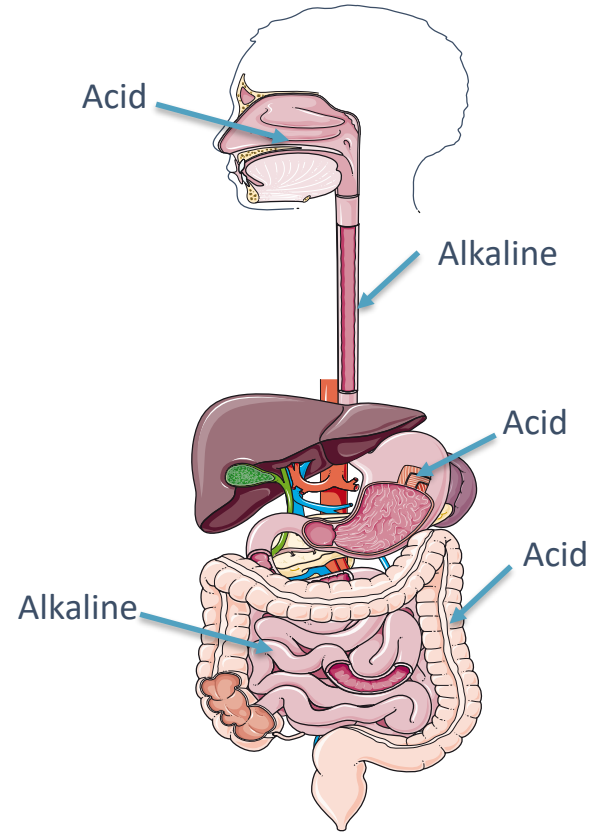
- Malnutrition
- Vitamin B<sub>12</sub> deficiency
- Anemia
- Poor absorption of fat
- Osteoporosis
- Kidney stones
- Damage to intestinal lining



# Probiotics for treating/ preventing SIBO

## Findings:

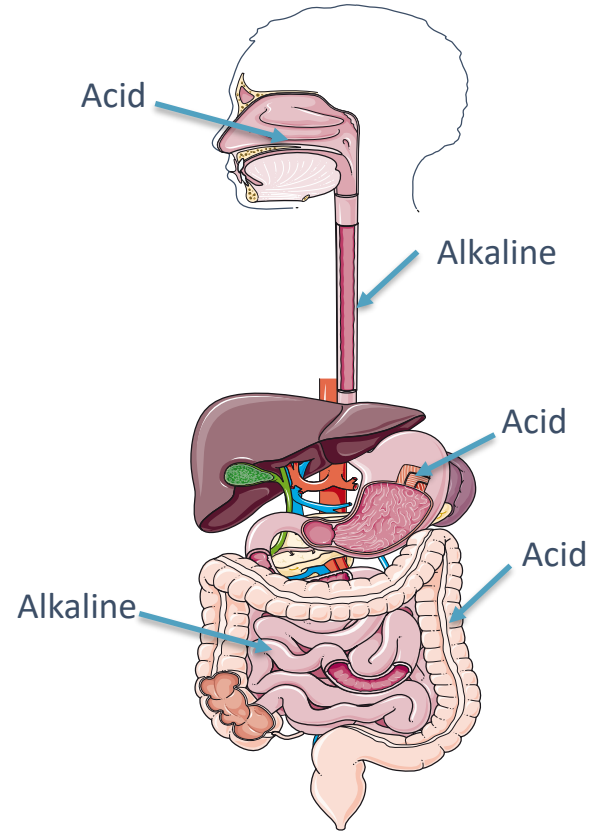
- Probiotic supplementation could effectively decontaminate SIBO
- Decrease H<sub>2</sub> concentration
- Relieve abdominal pain
- **Pooled analysis found probiotics remarkably effective for treatment of SIBO**



# SIBO protocol

## Phase I – 30 days

- Aromatic oils:
  - Kills bad bugs
  - Cleanses bowel of bacteria/viruses/yeast/parasites
- Berberine:
  - Cleanses GI tract by removing bacteria/viruses/yeast/parasites
- Bile salts and bitter extracts:
  - Helps body break down fats in the diet
  - Supports fat digestion and healthy liver/gallbladder function



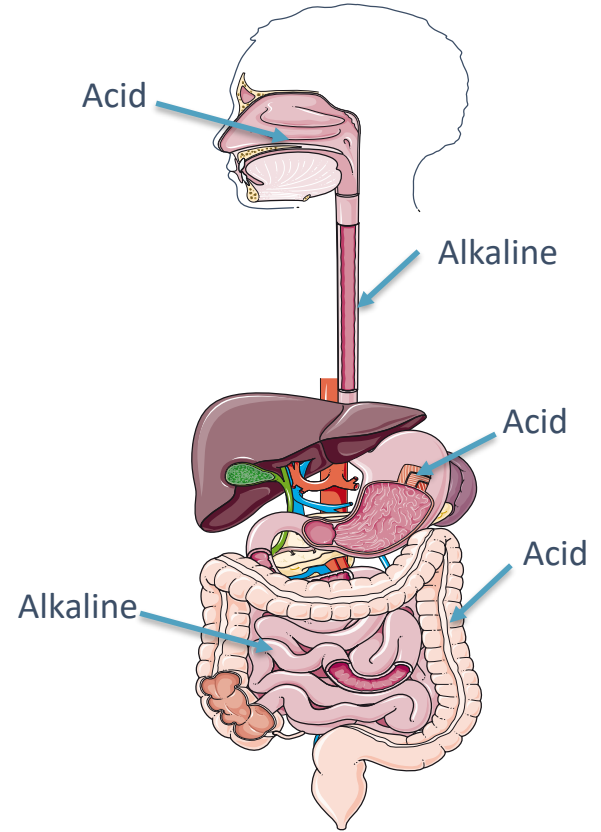
# SIBO protocol (cont'd)

## Phase I – 30 days (cont'd)

- Zinc carnosine (on empty stomach):
  - Enhances repair of stomach lining
- FODMAP elimination diet—avoid fructose, lactose, fructans, galactans, polyols

Or

- Ketogenic diet—no more than 50 g of carbs a day

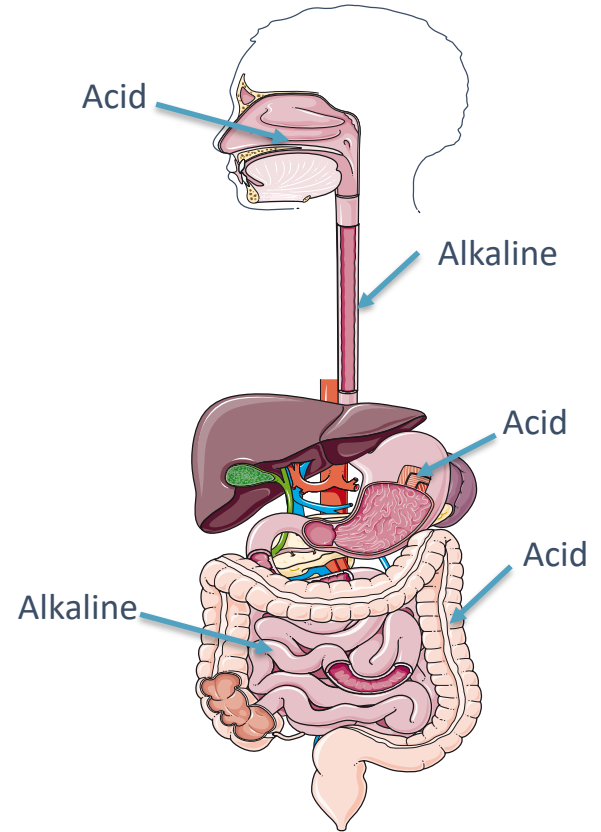




# SIBO protocol (cont'd)

## Phase II – 30 days

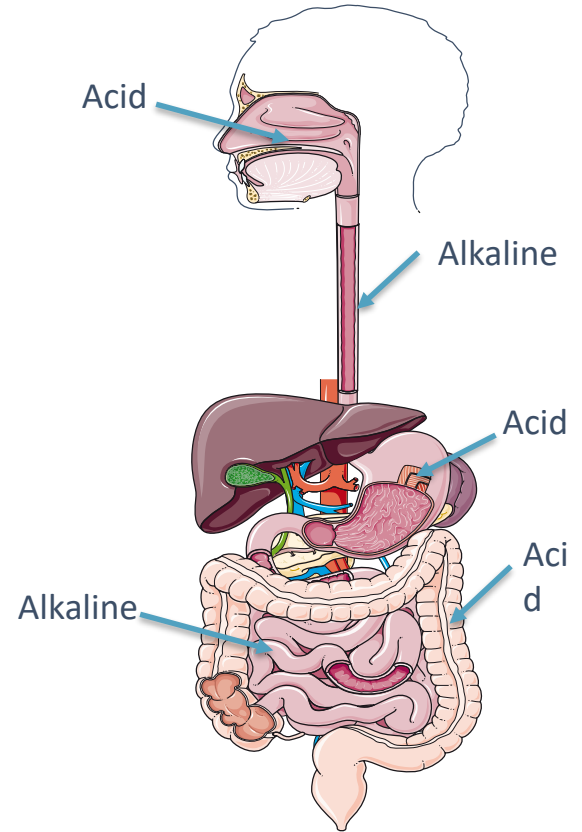
- Betaine HCl and pepsin:
  - Supports digestion and breakdown of food
- Broad spectrum of enzymes including acid stable lipase and 3 proteases that function in different pH ranges
- Continue with bile salts and bitter extracts



# SIBO protocol (cont'd)

## Phase II – 30 days (cont'd)

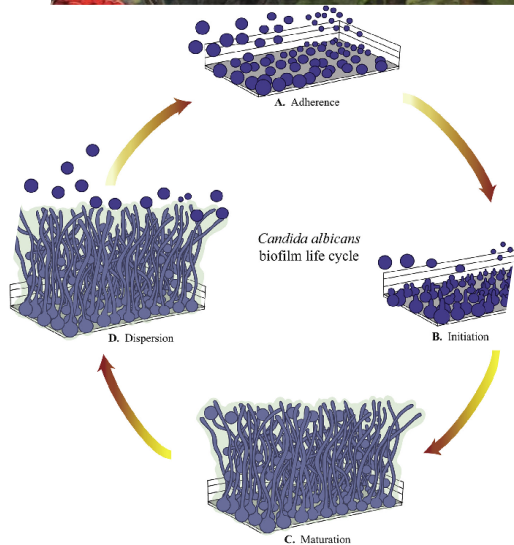
- Strain specific probiotics based on symptoms to support digestion
  - Short-chain fatty acid (SCFA) production
- Prebiotic nutritional support:
  - Soluble fiber
- Keto/elimination diet

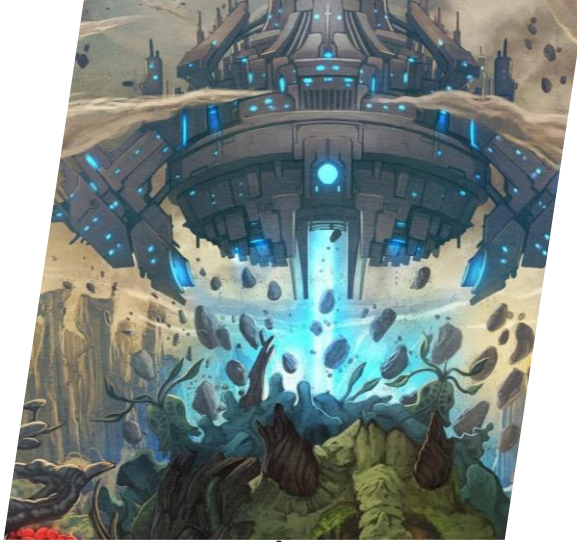




# Sub clinical infection Fungus—*Candida*

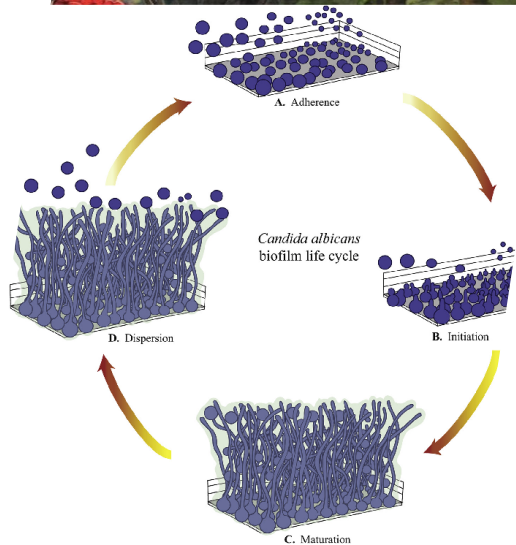
- Hard to test for and treat
  - They adhere to vascular and digestive linings
  - They communicate physically and chemically
  - They burrow into tissue and lie dormant
  - Anchor between the cells





# Sub clinical infection Fungus—*Candida*

- Overgrowth will occur
  - Acidic environment
  - Poor microbiota
  - Antibiotics
  - Medications
  - BCPs, HRTs
  - Surgeries
  - Processed water (i.e. tap)





# Sub clinical infection Fungus—*Candida*

- What they like
  - SUGAR!!!!
  - Braces, retainers
  - Surgical implants
  - Iron
  - Collagen
  - Hyaluronic acid
  - Synovial fluid



## Sub clinical infection Fungus—*Candida*

- Terra form to survive and thrive
  - Constant immune response
  - Maintains acidic environment
  - Perpetual stress hormones
  - Mitochondrial derailment
  - Catabolic
- Hard to kill
  - Bio-Film
  - Release spores before they die





# Sub clinical infection

## Fungus—*Candida*

- Neurotransmitters
  - Inhibits tryptophan to 5-HTP
    - Uncontrolled cravings
    - Not willpower—chemistry
  - Inhibits tyrosine to dopamine
    - Low conversion to epi/nor-EPI
    - Can't fight off infection
- Oxalates crystals
  - Further increase inflammation
  - Form stone
  - ADD, ADHD, autism spectrum



# Sub clinical infection Fungus—*Candida*

- History
  - 13 y/o
  - Obese since 7 y/o
  - Ear infections at 5 y/o
  - Stanford endocrinologist
  - Athlete
  - 3.5 month protocol
  - Did not realize the pain he was in



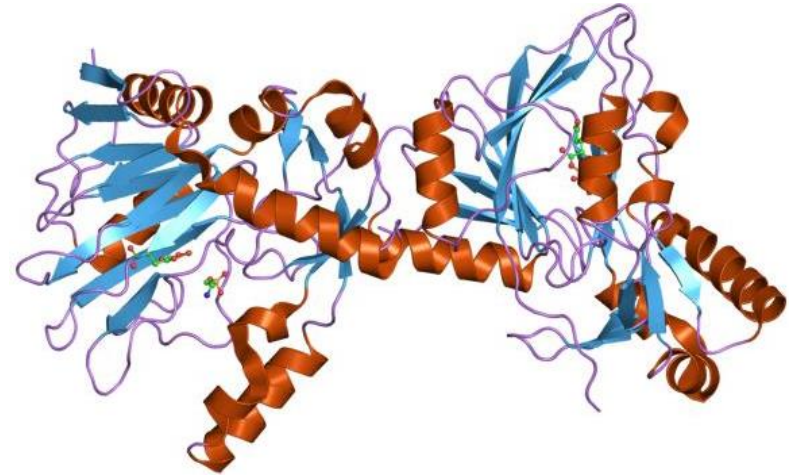


# Taurine—biological roles

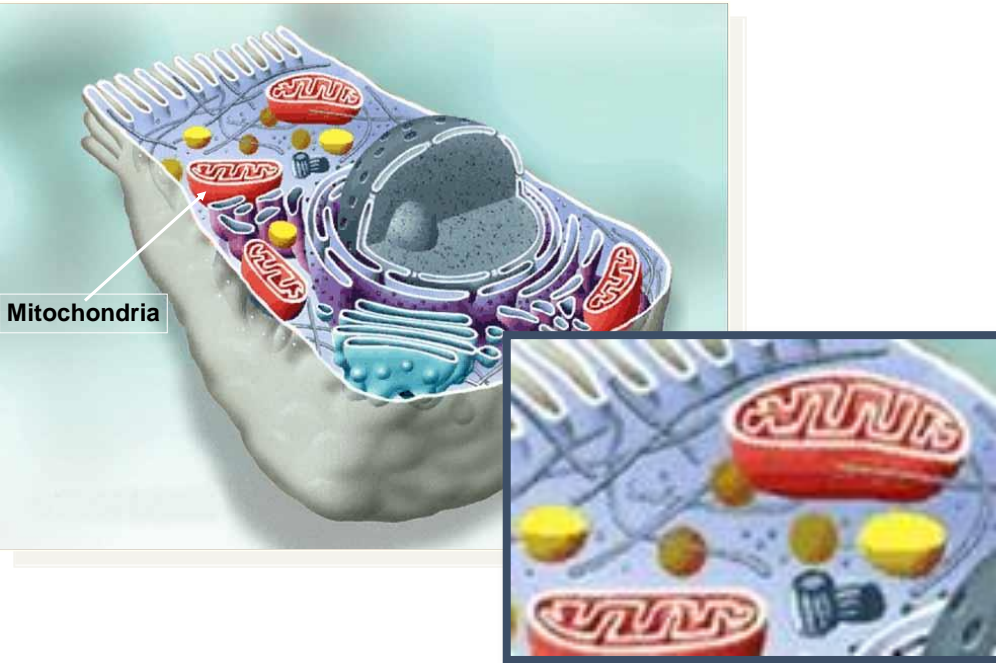
## Multi-dimensional support for mitochondrial-rich organ systems

### **Taurine** in the CNS

- A neuro-modulator
- An osmoregulator
- Regulates cytoplasmic calcium levels
- A neuroprotectant
- *Prevent mitochondrial dysfunction*



# Magnesium and mitochondrial function



Magnesium is an essential element that catalyzes more than 300 enzymatic reactions, ***in particular those involving mitochondrial ATP***

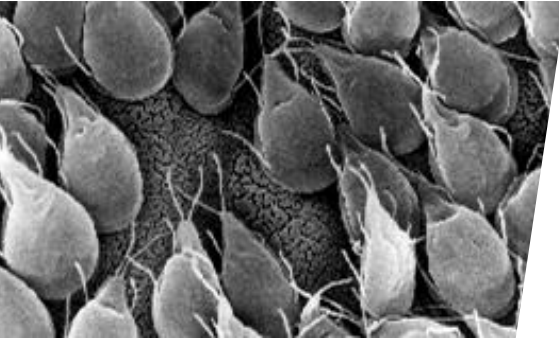
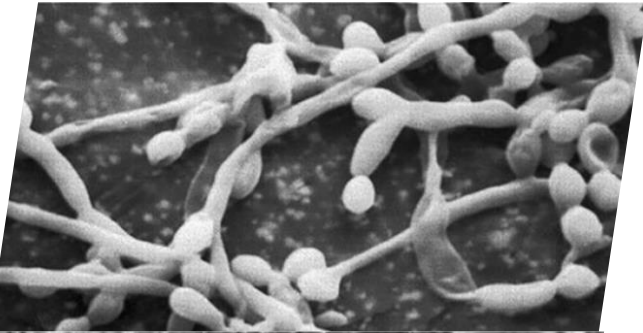
Mitochondrial Mg deficiency may increase excitatory events in the neuron

- ▶ Reduced ATP efficiency
- ▶ Calcium influx
- ▶ Excess glutamate
- ▶ Potentiate stimuli that trigger apoptosis (cell death)

Miller S., et al. *Heart*. 2005;91(5):618-623.

Gums JG. *Am J Health Syst Pharm*. 2004;61(15):1569-1576.

*J Clin Psychiatry*. 2000;61(Suppl 12):22-27.



# *Candida* protocol

- Concentrated aromatic oils
- Berberine complex
- Digestive enzymes
- *Saccharomyces boulardii*
- Prebiotic fiber
- Lipotropic formula
- Magnesium and taurine
- Xanthohumol
- Curcumin

Mechanistic research

# Fasting: nationally recognized science

“There is considerable similarity between how cells respond to the stress of exercise and how cells respond to intermittent fasting”

– Mark Mattson

(Collier, 2013)



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**NIH Public Access**  
**Author Manuscript**  
*Cell Metab.* Author manuscript; available in PMC 2015 February 04.

Published in final edited form as:  
*Cell Metab.* 2014 February 4; 19(2): 181–192. doi:10.1016/j.cmet.2013.12.008.

**Fasting: Molecular Mechanisms and Clinical Applications**

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<sup>3</sup>Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA

**Abstract**

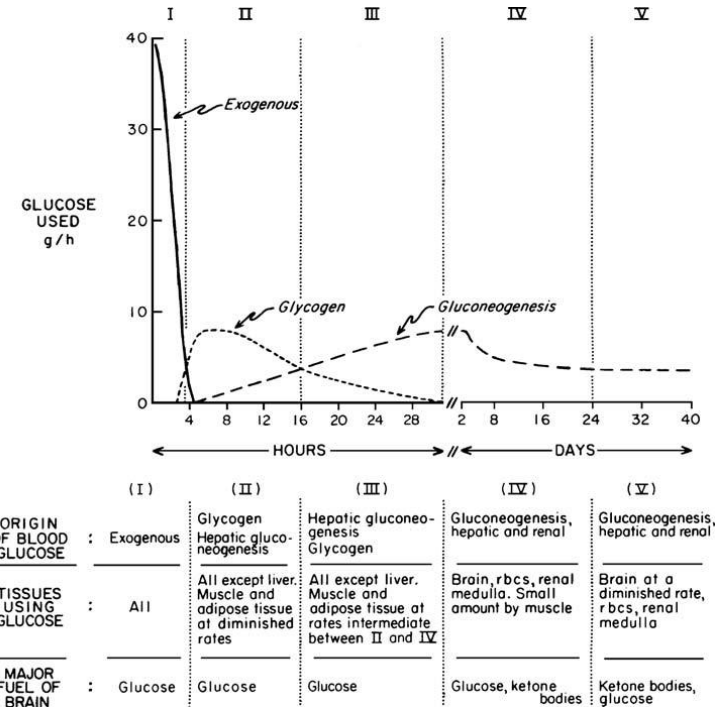
Fasting has been practiced for millennia, but only recently studies have shed light on its role in adaptive cellular responses that reduce oxidative damage and inflammation, optimize energy metabolism and bolster cellular protection. In lower eukaryotes, chronic fasting extends longevity in part by reprogramming metabolic and stress resistance pathways. In rodents intermittent or periodic fasting protects against diabetes, cancers, heart disease and neurodegeneration, while in humans it helps reduce obesity, hypertension, asthma and rheumatoid arthritis. Thus, fasting has the potential to delay aging and help prevent and treat diseases while minimizing the side effects caused by chronic dietary interventions.

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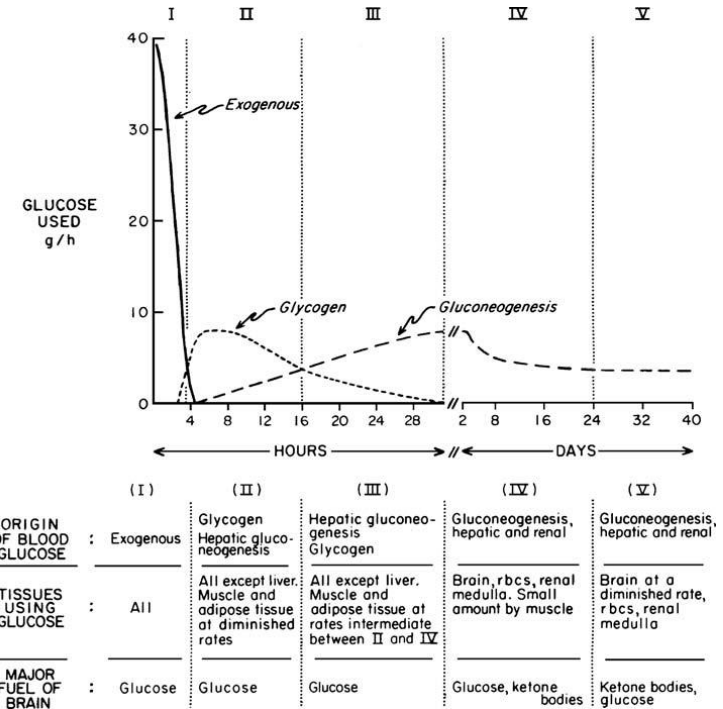
# Biological fasting occurs within 10-20 hrs of last intake of nutrition

- This is due to the depletion of hepatic glucose stores
  - Stage I absorptive/post-prandial
  - Stage II post-absorptive
  - Stage III early starvation or fasting
  - Stage IV intermediate fasting
  - Stage V prolonged fasting



# Stages of therapeutic fasting

- I Absorptive/Post-Prandial
  - 1-6 hours
  - Increase insulin
  - Increase glucose uptake
    - Muscle, organ, brain
      - Direct use of energy
  - Increase muscle and liver glycogen
  - Excess stored
    - Visceral or subcutaneous fat



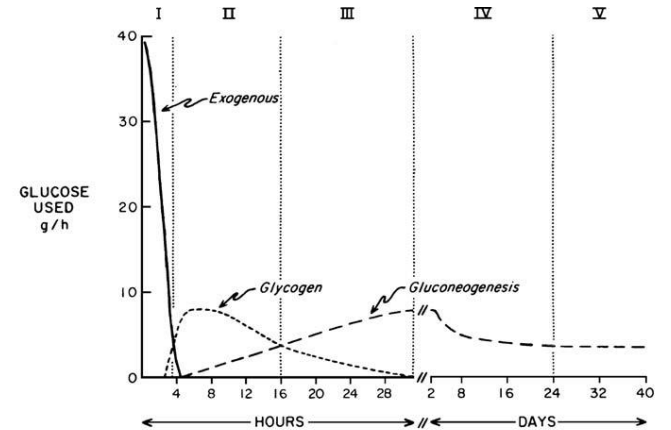
# Stages of therapeutic fasting

- II Post Absorptive Phase

- 6- 24 hours fasting
- Insulin levels fall
- Breakdown of glycogen to glucose
- Glycogen storage  $\approx$ 24 hours

- III Gluconeogenesis

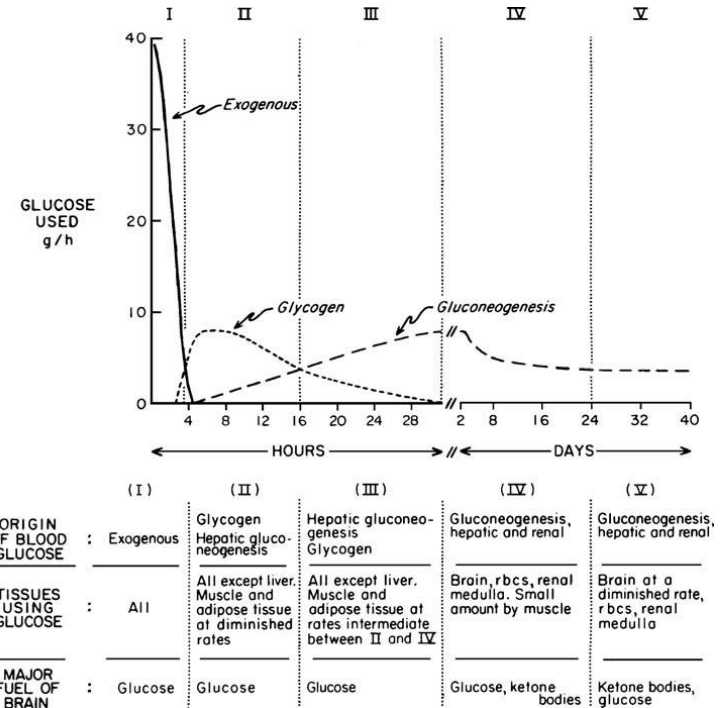
- 24-48 hrs
- Liver makes new glucose from amino acids and glycerol
- Glucose falls WNL for non-diabetics



	(I)	(II)	(III)	(IV)	(V)
ORIGIN OF BLOOD GLUCOSE	Exogenous	Glycogen Hepatic gluconeogenesis	Hepatic gluconeogenesis Glycogen	Gluconeogenesis, hepatic and renal	Gluconeogenesis, hepatic and renal
TISSUES USING GLUCOSE	All	All except liver. Muscle and adipose tissue at diminished rates	All except liver. Muscle and adipose tissue at rates intermediate between II and IV	Brain, rbc's, renal medulla. Small amount by muscle	Brain at a diminished rate, rbc's, renal medulla
MAJOR FUEL OF BRAIN	Glucose	Glucose	Glucose	Glucose, ketone bodies	Ketone bodies, glucose

# Stages of therapeutic fasting

- IV Ketosis - 24-72 hrs
  - Triglycerides break down from fat
    - Glycerol backbone
    - 3 fatty acid chains
  - Glycerol used for gluconeogenesis
  - Fatty acids for energy (except the brain)
  - Fatty acids breakdown to ketones
  - Ketones cross the BBB
    - Acetoacetate
    - BHB (70(X) increase during fasting)

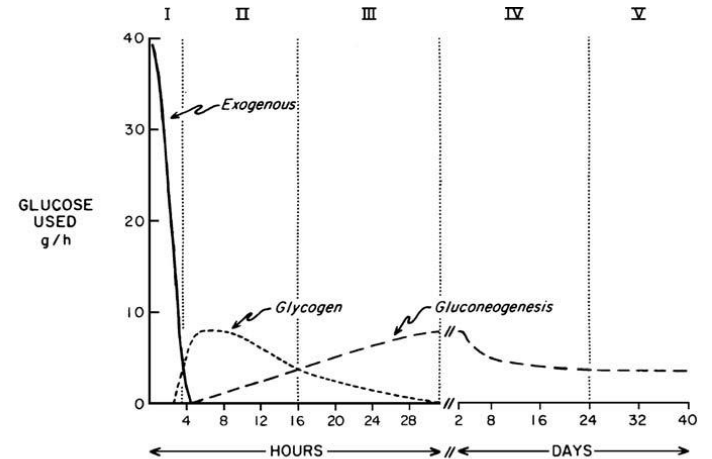




# Stages of therapeutic fasting

- V Prolonged fasting (post 5 days)

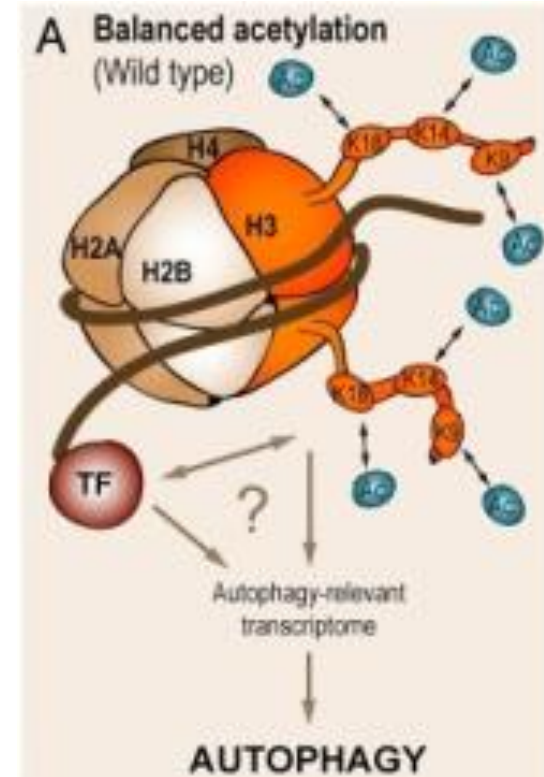
- Protein conservation
  - Increase growth hormones
- Free fatty acids and ketones meet energy requirements
- Insulin lowered
- Growth hormone increased
  - Can double with 5 day fast
- Adrenalin increase (to find food)
  - Starts at 24 hours
  - 48 hours- 3.6% increase
  - 4 day fast
    - BMR can increase 14%
  - Opposite with caloric restriction
    - Adrenalin goes down



	(I)	(II)	(III)	(IV)	(V)
ORIGIN OF BLOOD GLUCOSE	Exogenous	Glycogen Hepatic gluconeogenesis	Hepatic gluconeogenesis Glycogen	Gluconeogenesis, hepatic and renal	Gluconeogenesis, hepatic and renal
TISSUES USING GLUCOSE	All	All except liver. Muscle and adipose tissue at diminished rates	All except liver. Muscle and adipose tissue at rates intermediate between II and IV	Brain, rbc's, renal medulla. Small amount by muscle	Brain at a diminished rate, rbc's, renal medulla
MAJOR FUEL OF BRAIN	Glucose	Glucose	Glucose	Glucose, ketone bodies	Ketone bodies, glucose

# Fasting promotes biochemical hormesis

- A controlled stressor that might activate the repair mechanisms of the body
- Autophagy
  - Cellular waste and dysfunctional proteins are recycled
- Apoptosis
  - Controlled cell death



Longo VD, et al. *Cell metabolism*. 2014;19(2):181-192. doi:10.1016/j.cmet.2013.12.008.

Ruetenik A, et al. *Biochimica et biophysica acta*. 2015;1847(11):1434-1447. doi:10.1016/j.bbabo.2015.05.005

Ohtsujii M, et al. *The Journal of Biological Chemistry*. 2008;283(48):33554-33562. doi:10.1074/jbc.M804597200.

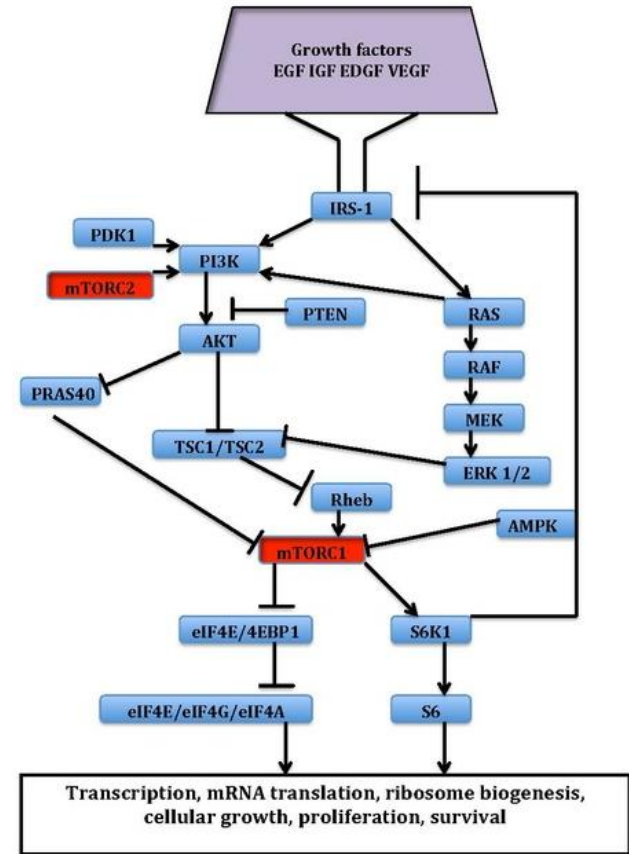
# Insulin sensitivity & cellular regeneration: mTORC1 and mTORC2

- mTORC1

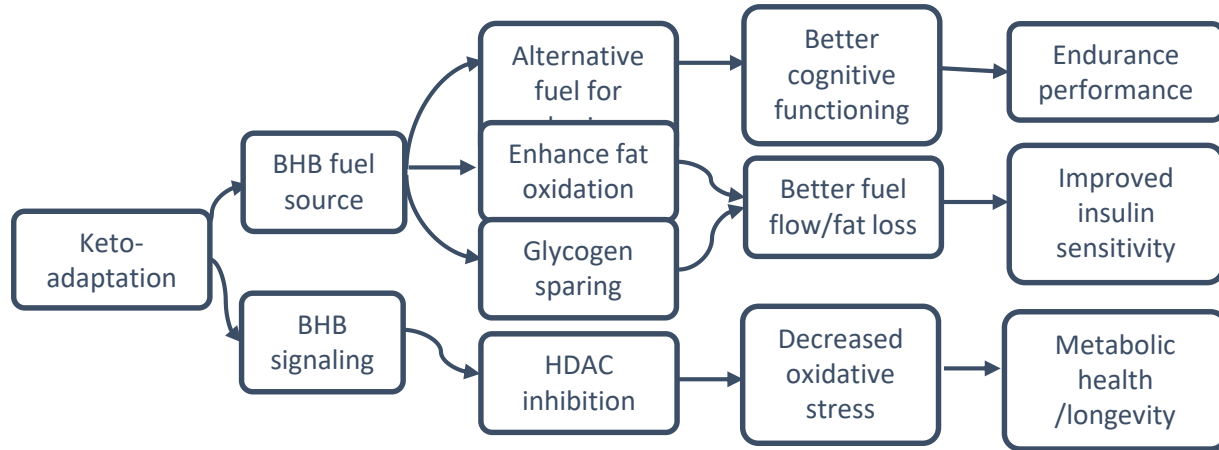
- Protein synthesis
- Ribosome biogenesis
- Transcription
- Autophagy

- mTORC2

- Actin fiber
  - Muscle contraction
  - Cell motility and division
  - Vesicle and organelle movement
  - Cell signaling
  - Maintenance of cell junctions
  - Cell structural integrity and shape



# In summary



Adapted from: Volek et al. *European Journal of Sport Science* 2015; 15(1):13-20

## Ketogenic diets:

- ✓ Increase liver fat oxidation
- ✓ Support weight management
- ✓ Improve insulin sensitivity
- ✓ Reduce hunger and increase both satiety and satiation
- ✓ Likely beneficial for cognition

## Ketone bodies:

- ✓ Efficient fuel source
- ✓ Improve mitochondrial bioenergetics
- ✓ Cellular signaling molecule
- ✓ Preserved uptake by the brain

Your future patients are dying to know what you know

