

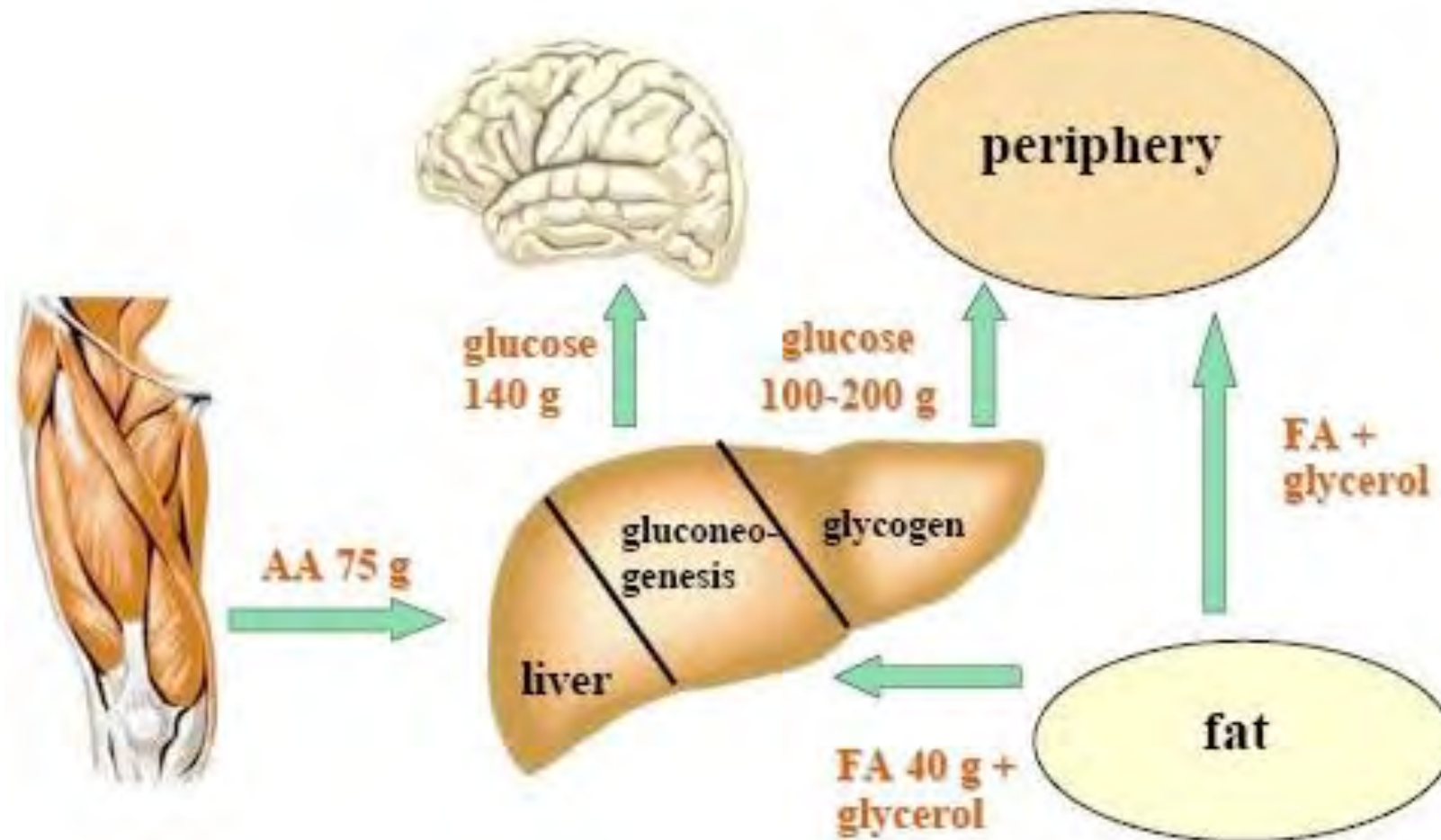
Ketogenic diet: using an ancient metabolic mechanism to treat inflammation today



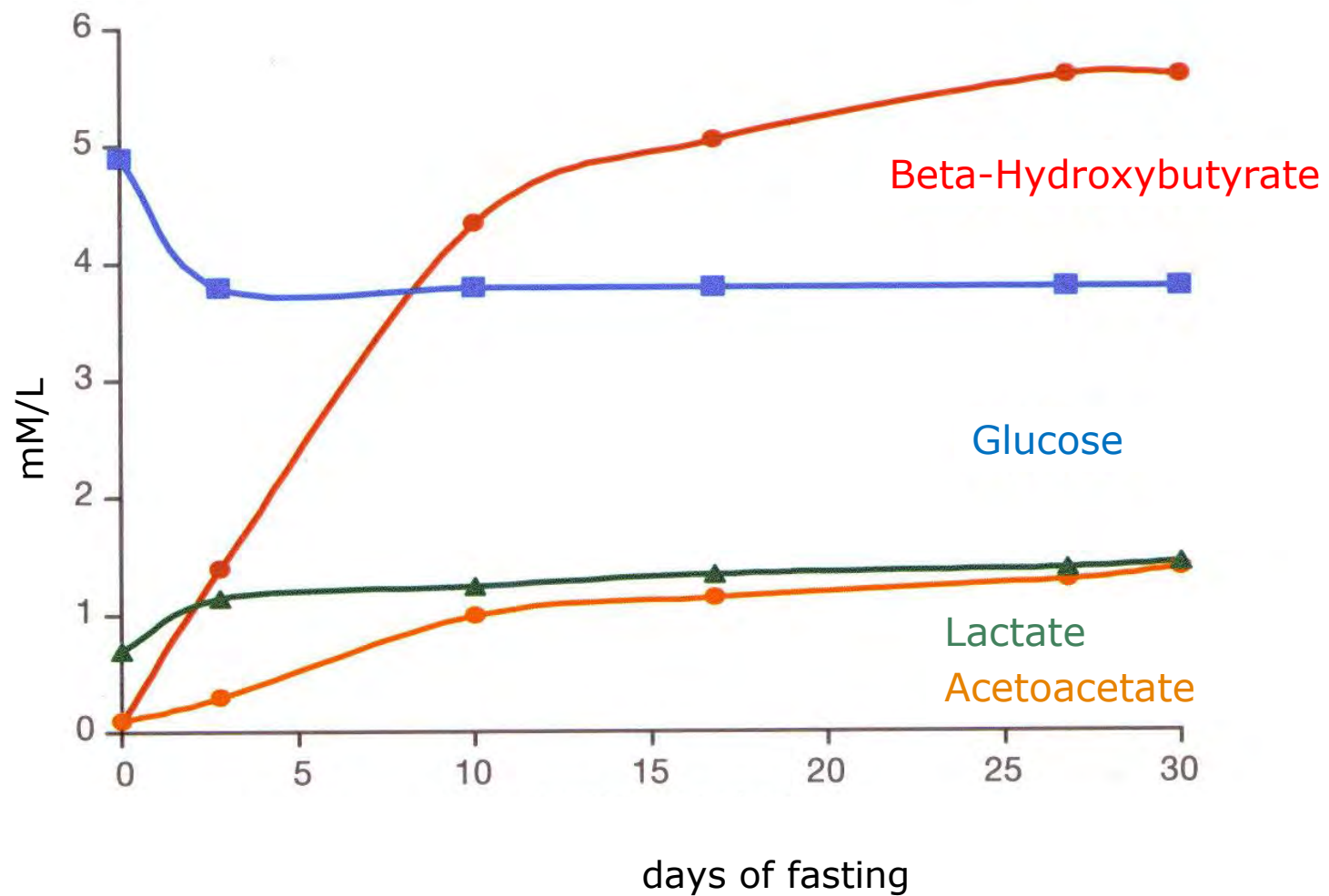
Prof. Dr. Dr. Simone Kreth
Klinik für Anaesthesiologie
Walter-Brendel-Zentrum für Experimentelle Medizin
LMU München

- **What is a ketogenic diet?**
- **What role do ketones play in the human body?**
- **What is the benefit of using ketones as fuel?**

Metabolism short-time Fasting

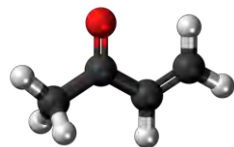


Metabolism long-time Fasting



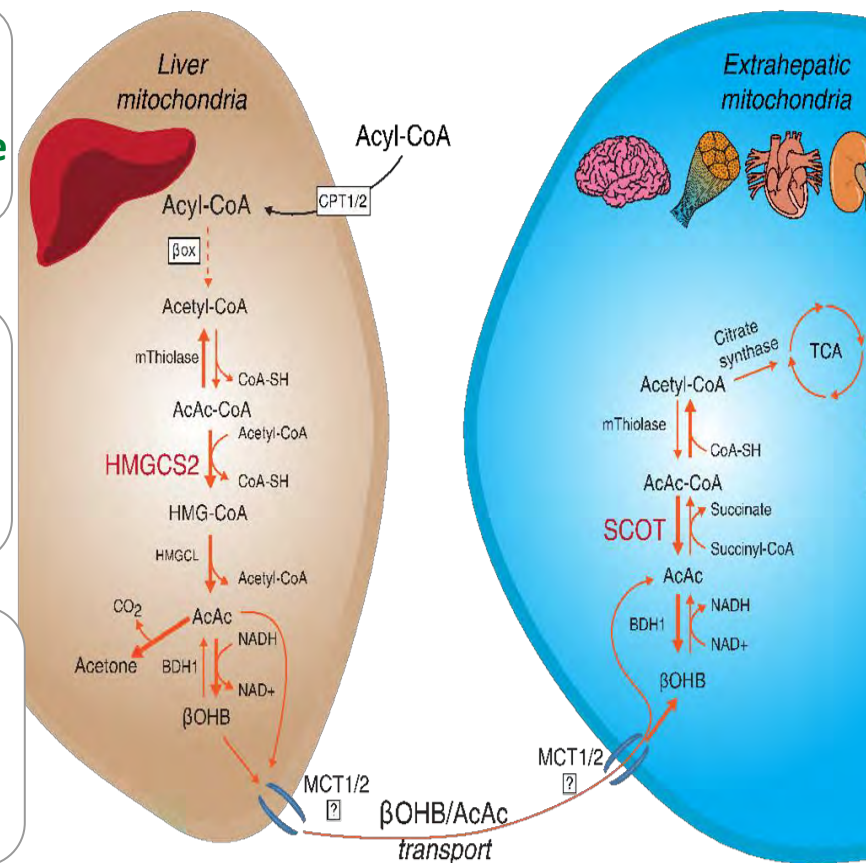
Ketone Bodies

Ketone bodies as energy source



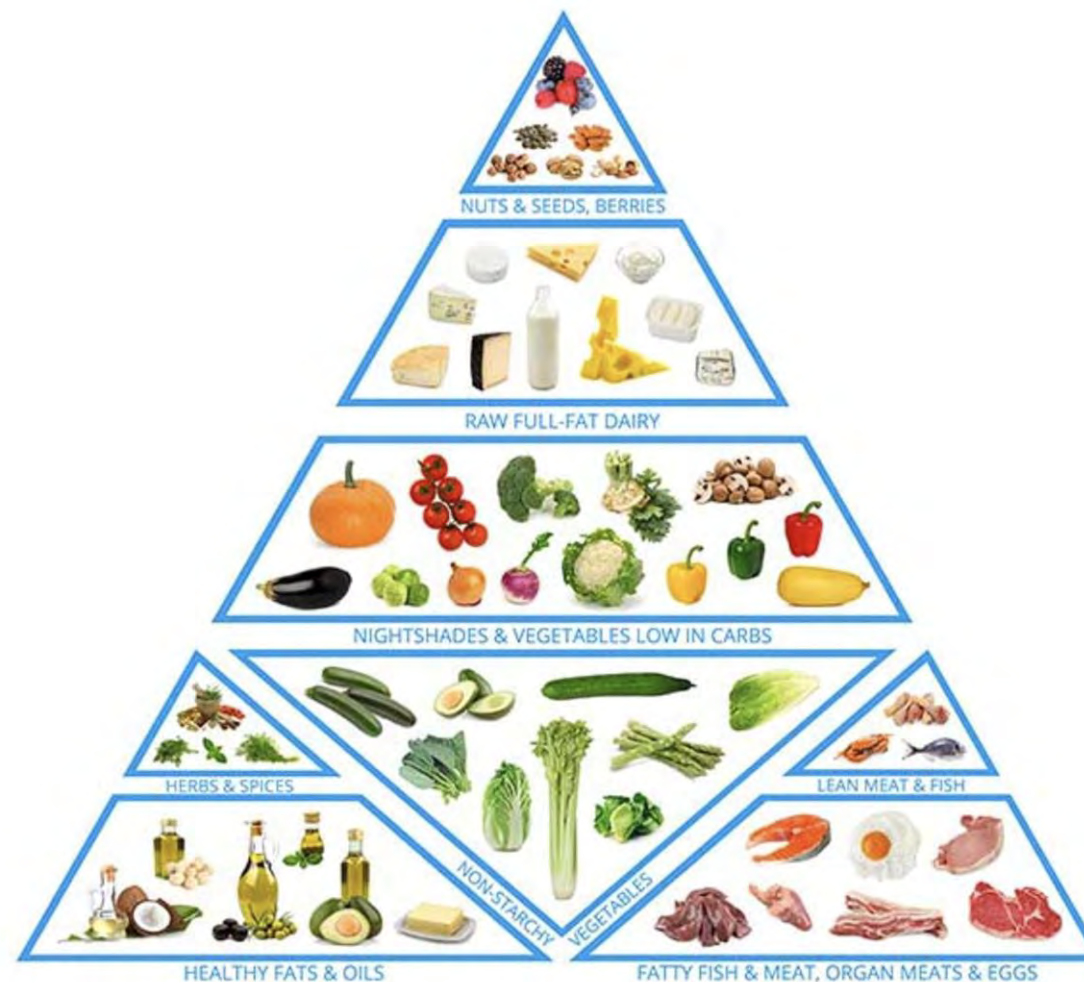
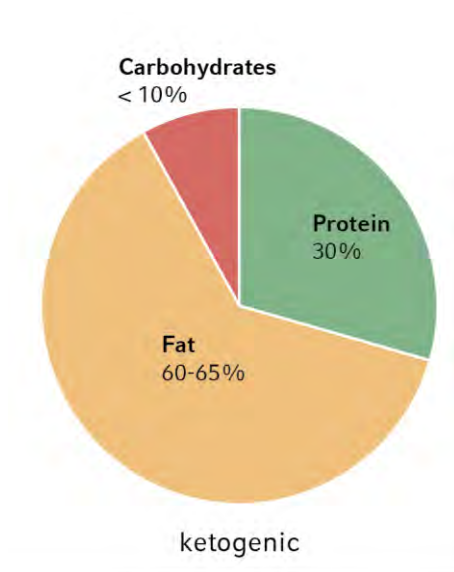
beta-Hydroxybutyrate (BHB)

- Synthesized from body or dietary fat
- Physiological source of energy in states of food deficiency
- Muscle mass is largely preserved
- Ancient evolutionarily conserved survival mechanism of mammals

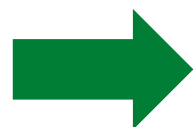


“Fasting mimicking diet” | Ketogenic Diet

<30g carbohydrates /day

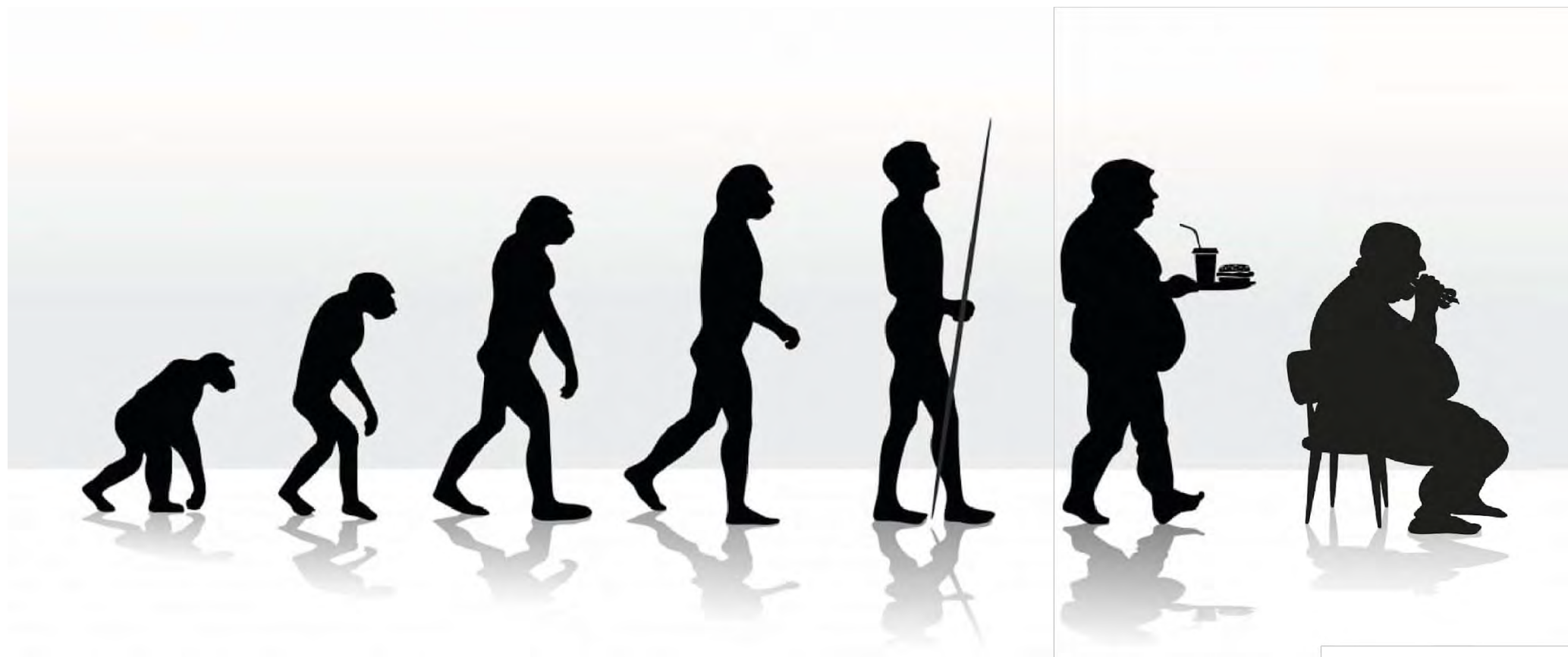


Why are we interested in this evolutionarily old metabolic pathway today?



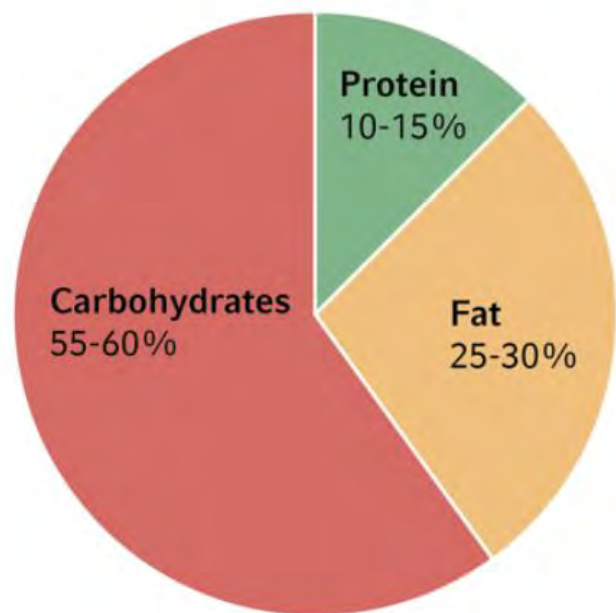
The metabolization of ketones offers benefits that might be useful in the treatment/prevention of "modern diseases"

Social development - Going Backwards?



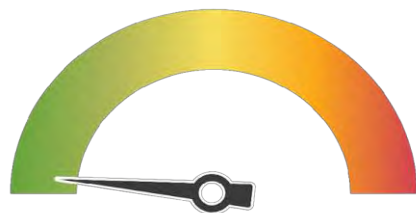
www.sway.com

Typical Western Diet



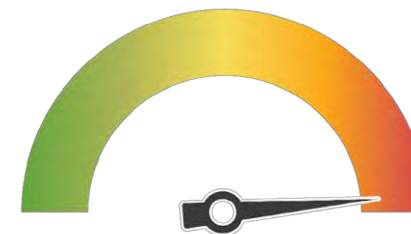
“Western diet” - Impact on immunity

Induction of NLRP3-mediated inflammation

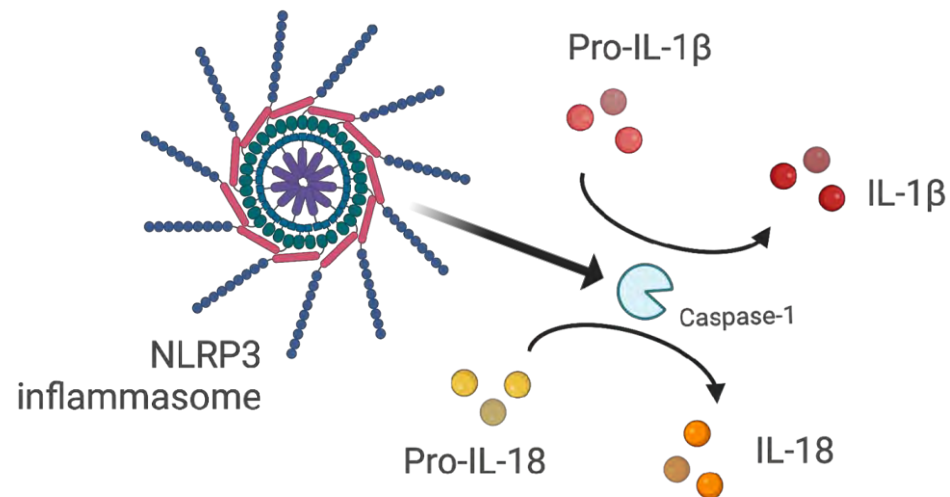


Homoestasis

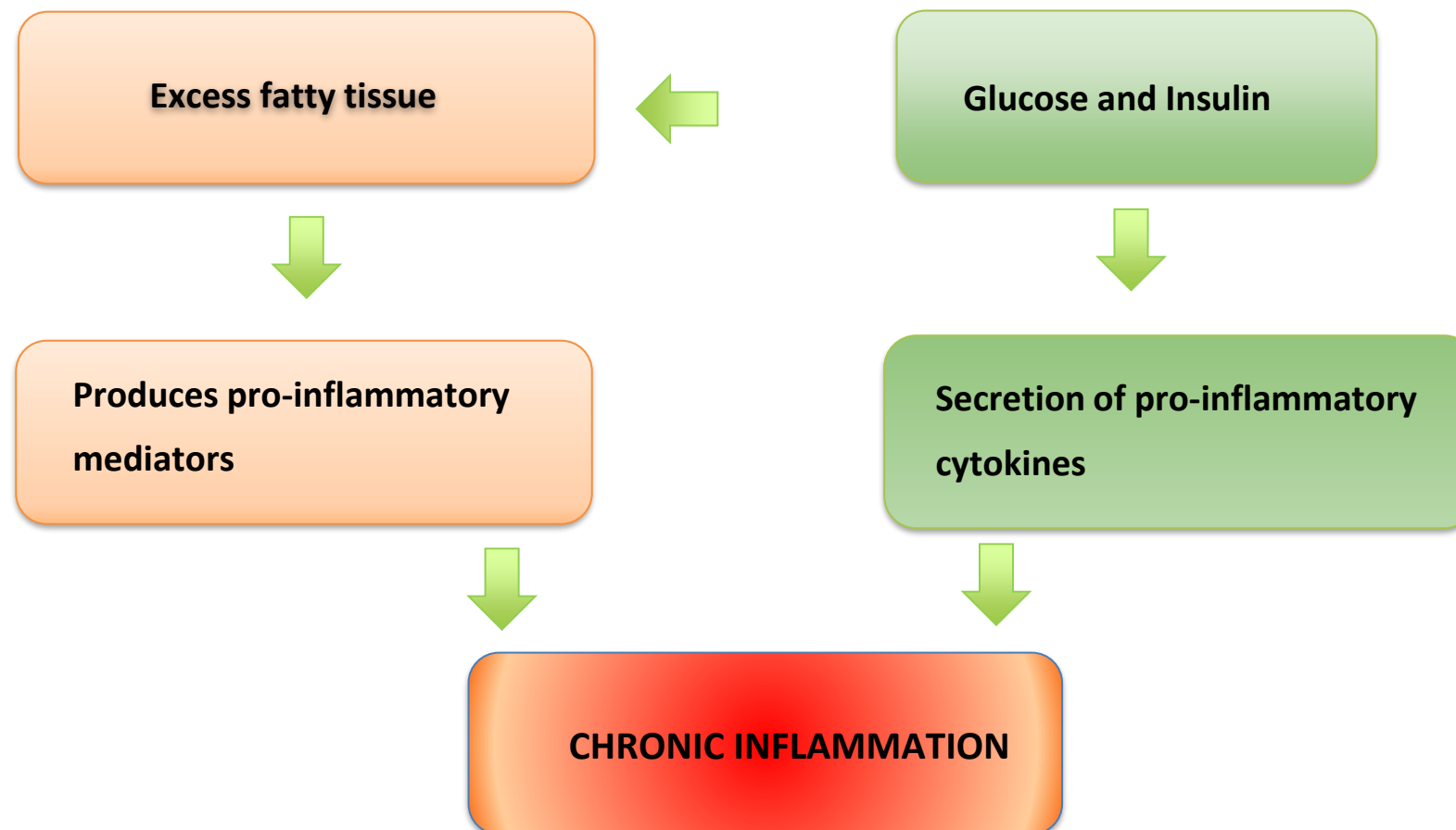
Western Diet with emphasis on
Glucose and Insulin



Inflammation

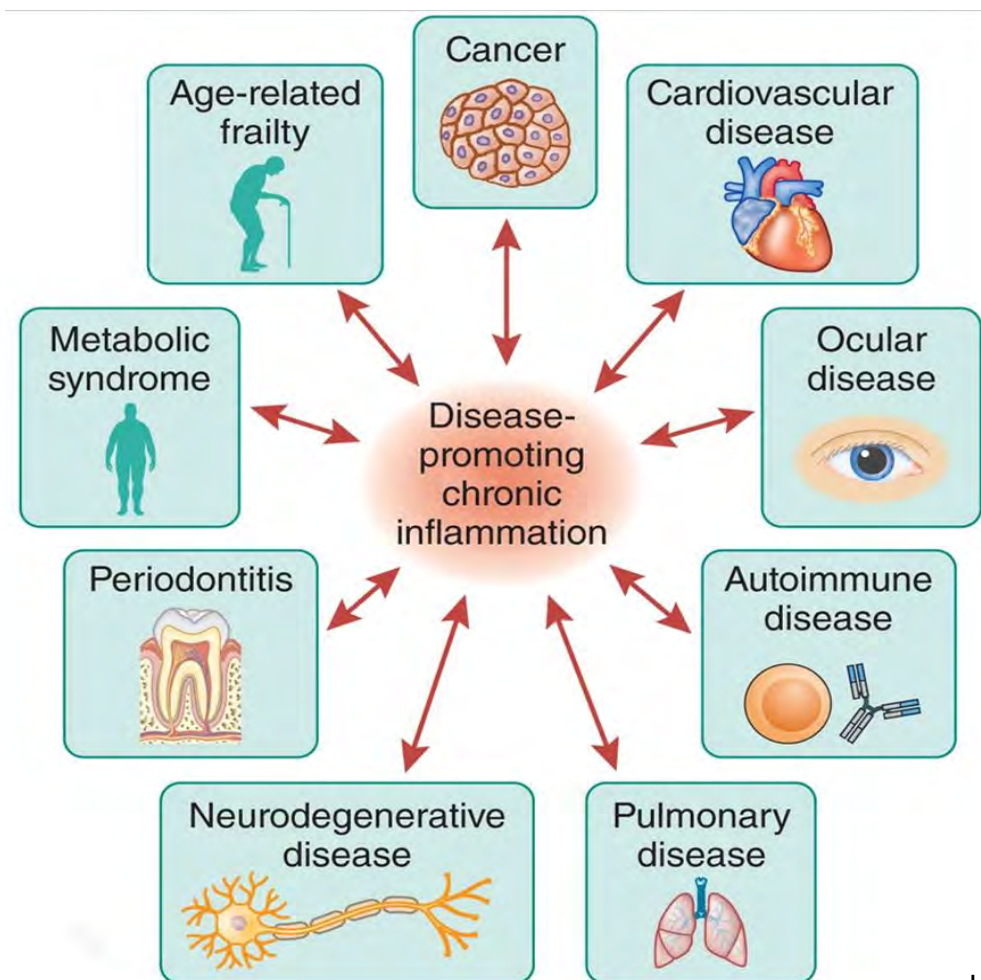


Consequences of Western Diet



“Western diet” - Impact on immunity

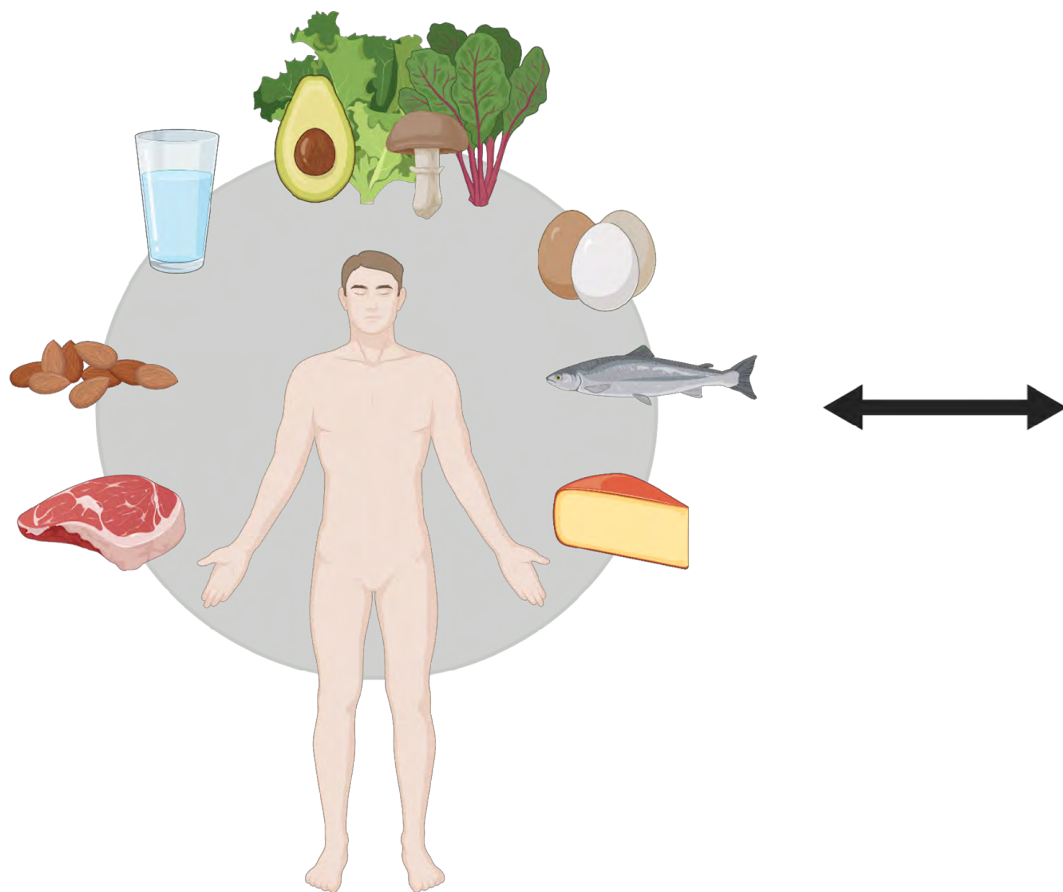
Promoting chronic inflammatory diseases



Liu et al, **Nature**, 2017

Chronic inflammation

Nutrition as a therapeutic tool?



Ketogenic diet in mouse models

Ketone bodies attenuate NLRP3-mediated inflammation

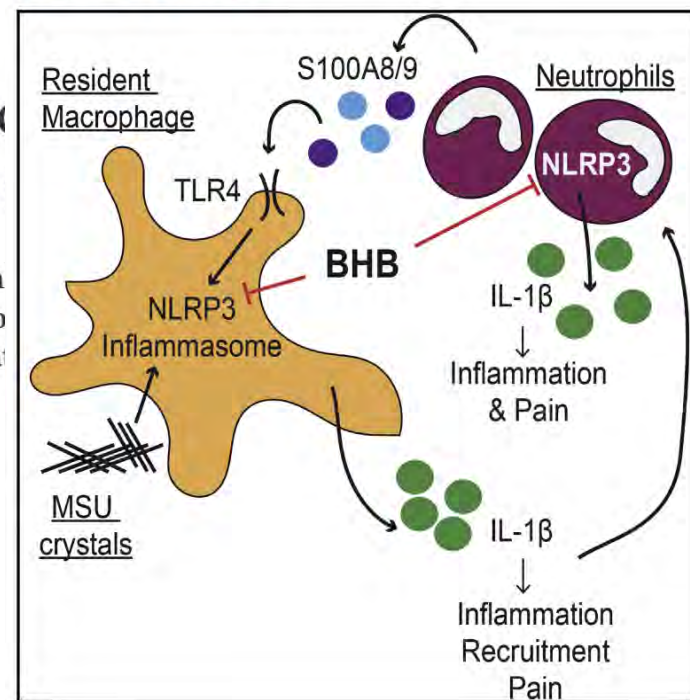
Report **TTTERS**

nature
medicin

Cell Reports

β -Hydroxybutyrate Deactivates Neutrophil NLRP3 Inflammasome to Relieve Gout Flares

Graphical Abstract



The keto
NLRP3

Yun-Hee Youm
Dominic D'Agostino
Tamas L Horvath

Authors

Emily L. Goldberg, Jennifer L. Asher, Ryan D. Molony, ..., Raimund I. Herzog, Akiko Iwasaki, Vishwa Deep Dixit

Correspondence

vishwa.dixit@yale.edu

In Brief

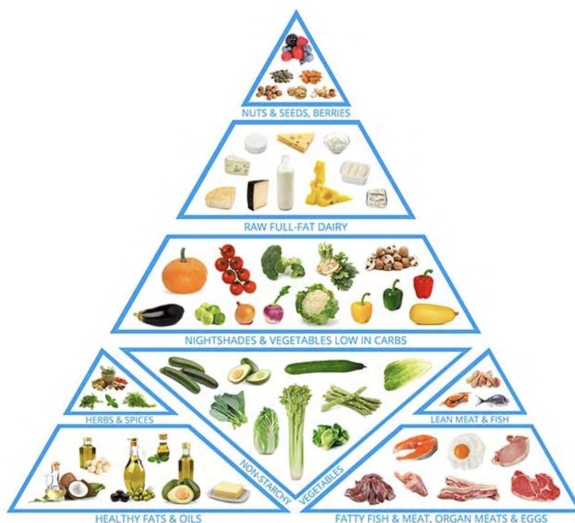
NLRP3 inflammasome activation in macrophages and neutrophils drives painful inflammation during gout. Goldberg et al. report that ketogenic diet prevents systemic inflammation and joint damage in a rat model of gouty flare. Mechanistically, the ketone body β -hydroxybutyrate, the most abundant ketone in vivo, inhibits NLRP3/caspase-1-dependent IL-1 β secretion from neutrophils.

ase

im⁴,
g⁸,
Dixit^{1,10}

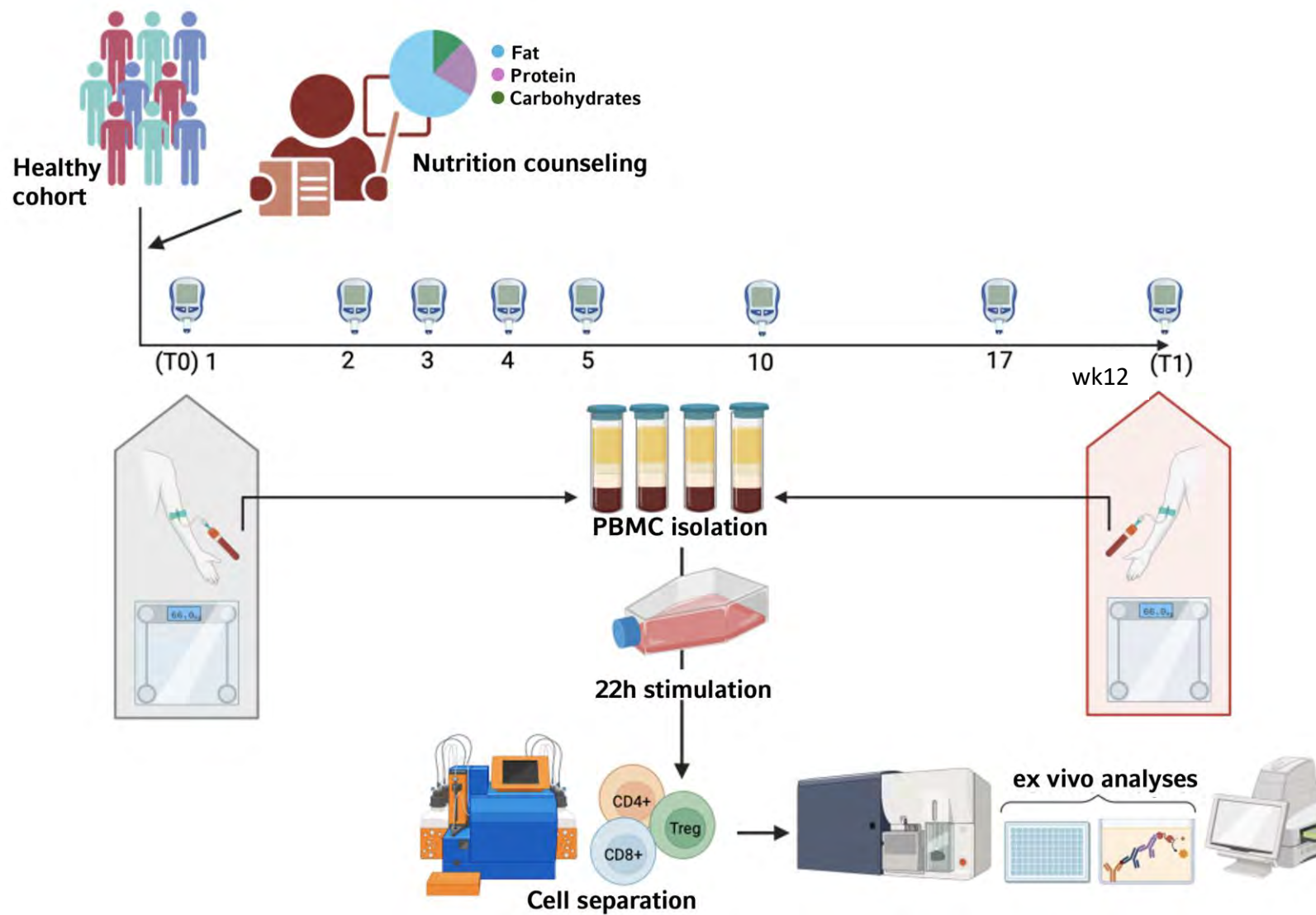
“Fasting mimicking diet” | Ketogenic Diet

In Humans: Effects? Side Effects?

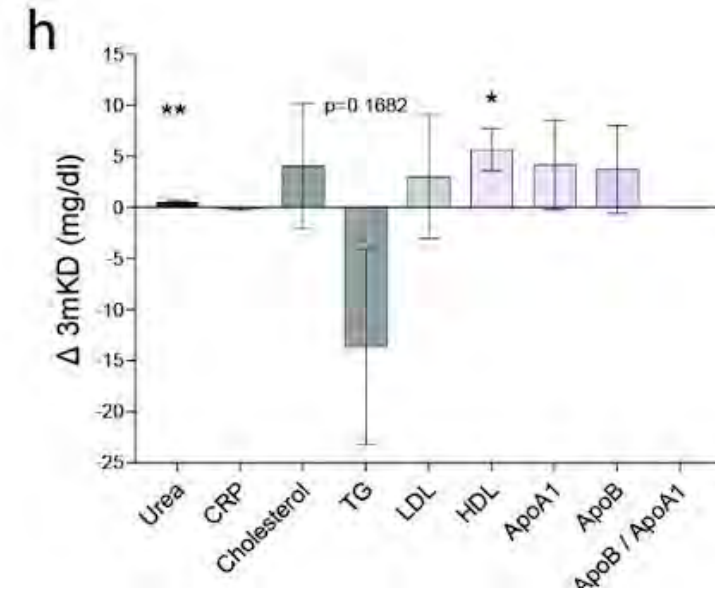
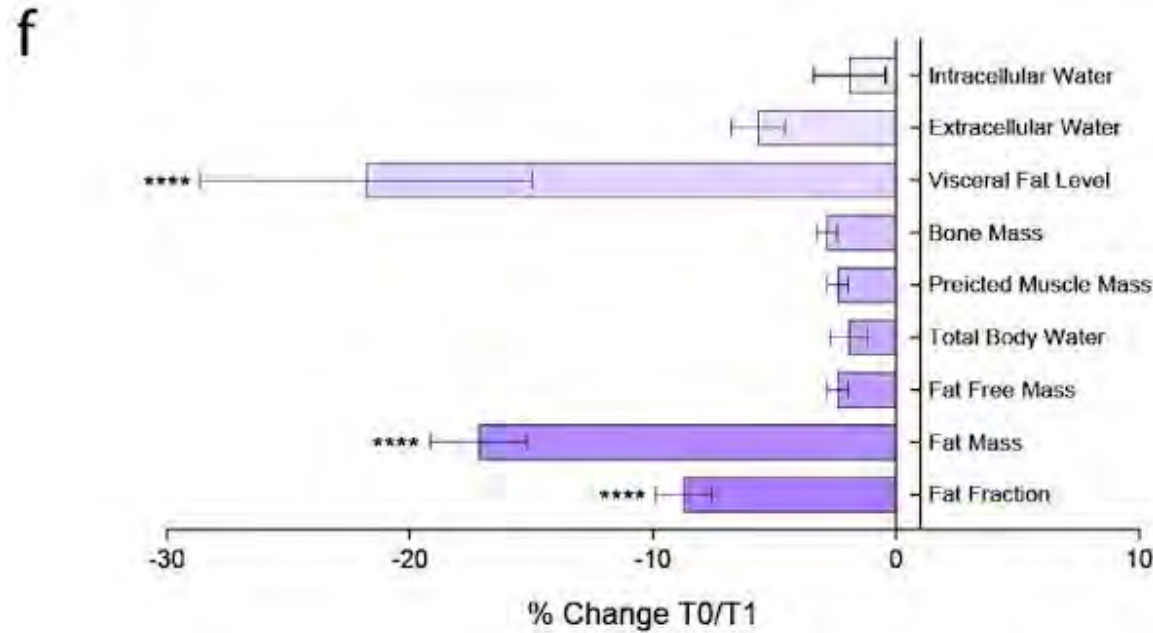
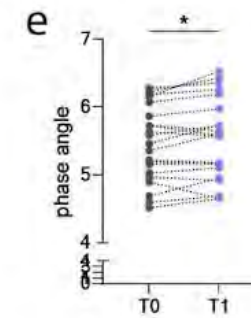
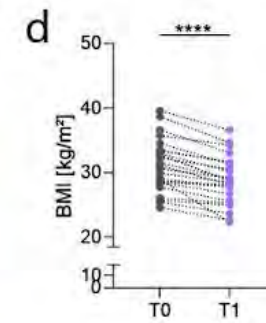
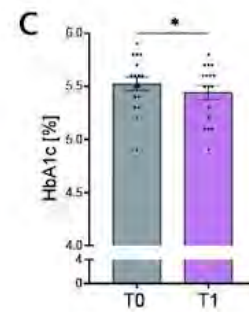
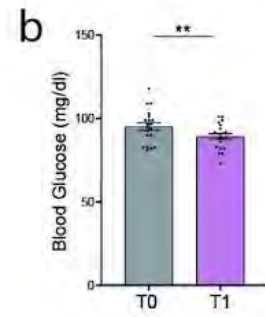
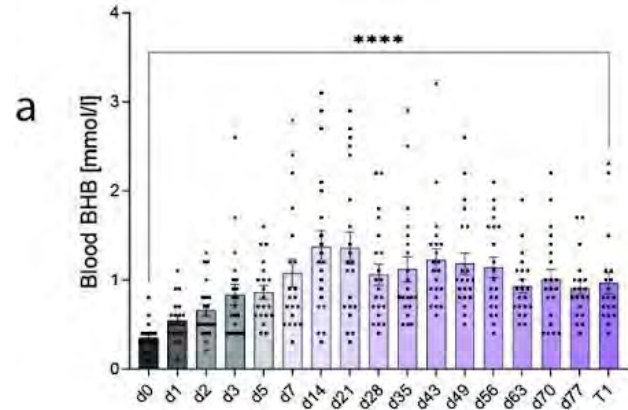


- **Metabolism**
- **General Well-being**
- **Body Composition**
- **Immune System**

Study Design



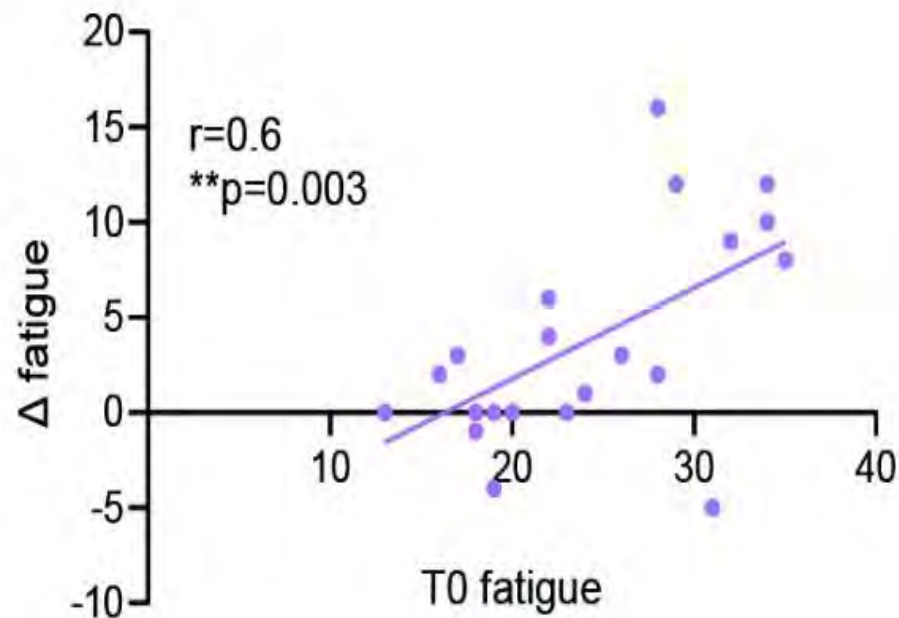
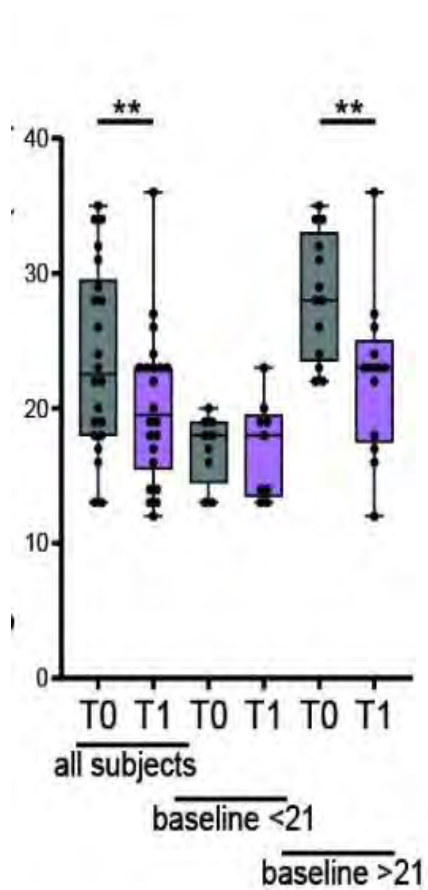
3- months KD: Positive effects on Metabolism and Body Composition



„Quality of life“ improves

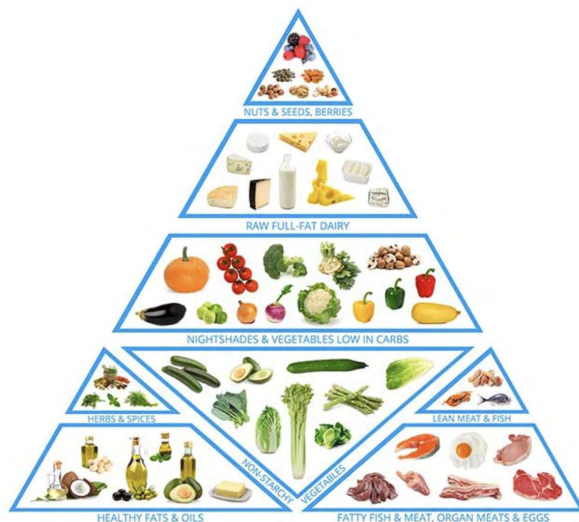
questionnaire in participants of three-month KD	Three-month KD	p-value
SF-36 (mean ± SEM), n=25		
•Physical functioning	+8.03 % ± 2.04 %	0.0002
•Physical role functioning	+14.81 % ± 6.91 %	0.0312
•Emotional role functioning	+20.00 % ± 9.02 %	0.0625
•Bodily pain	+14.73 % ± 4.77 %	0.0078
•Mental health	+21.30 % ± 5.59 %	0.0002
•Social role functioning	+15.33 % ± 7.28 %	0.0371
•General health perception	+11.11 % ± 4.17 %	0.0133
•Vitality	+35.64 % ± 8.66 %	0.0002
WHOQOL-BREF, (mean ± SEM), n=25		
•Physical health	+13.91 % ± 4.11 %	0.0026
•Mental health	+13.57 % ± 3.95 %	0.0023
•Social relationships	+7.07 % ± 2.95 %	0.0262
•Environmental quality	+4.19 % ± 1.64 %	0.0180

Fatigue symptoms are reduced after 3 months of ketogenic KD



“Fasting mimicking diet” | Ketogenic Diet

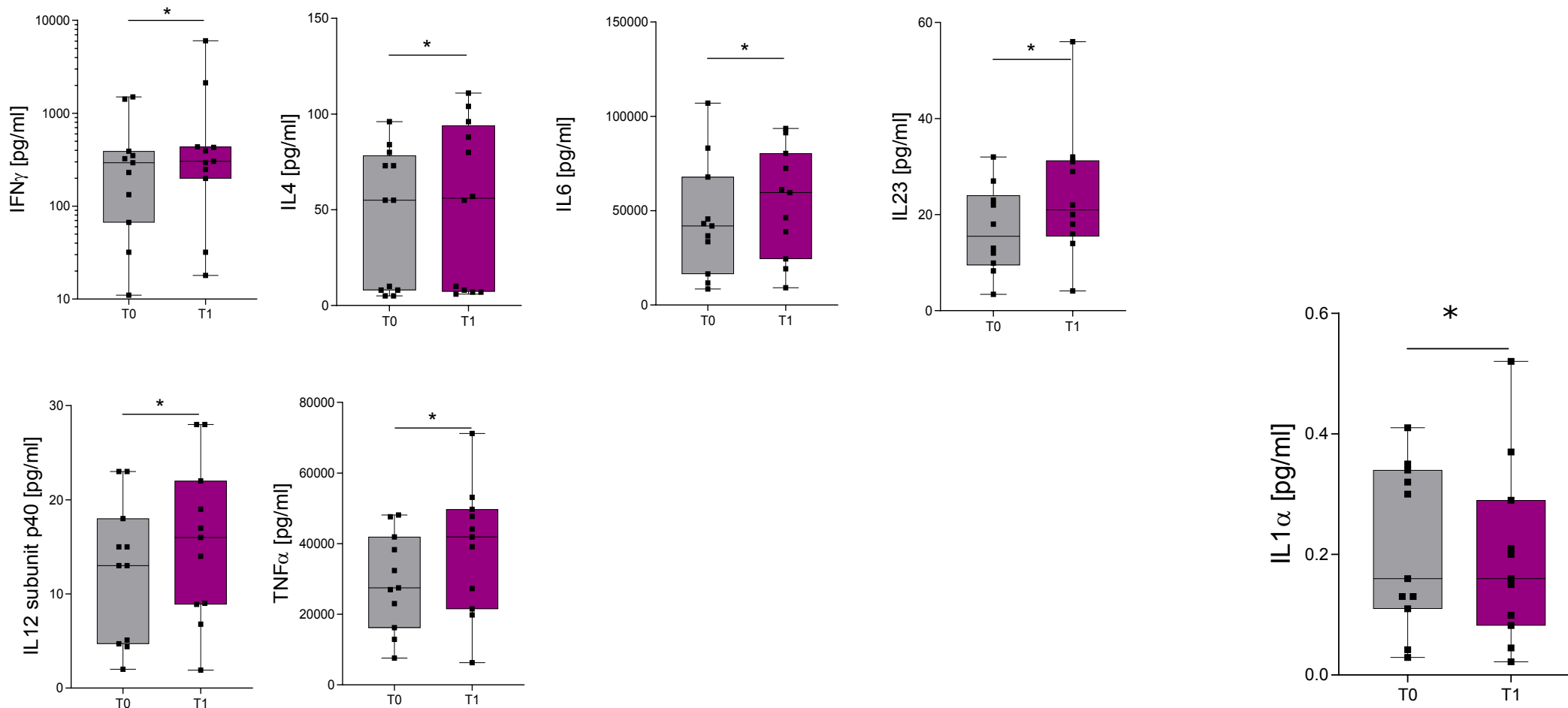
In Humans: Effects? Side Effects?



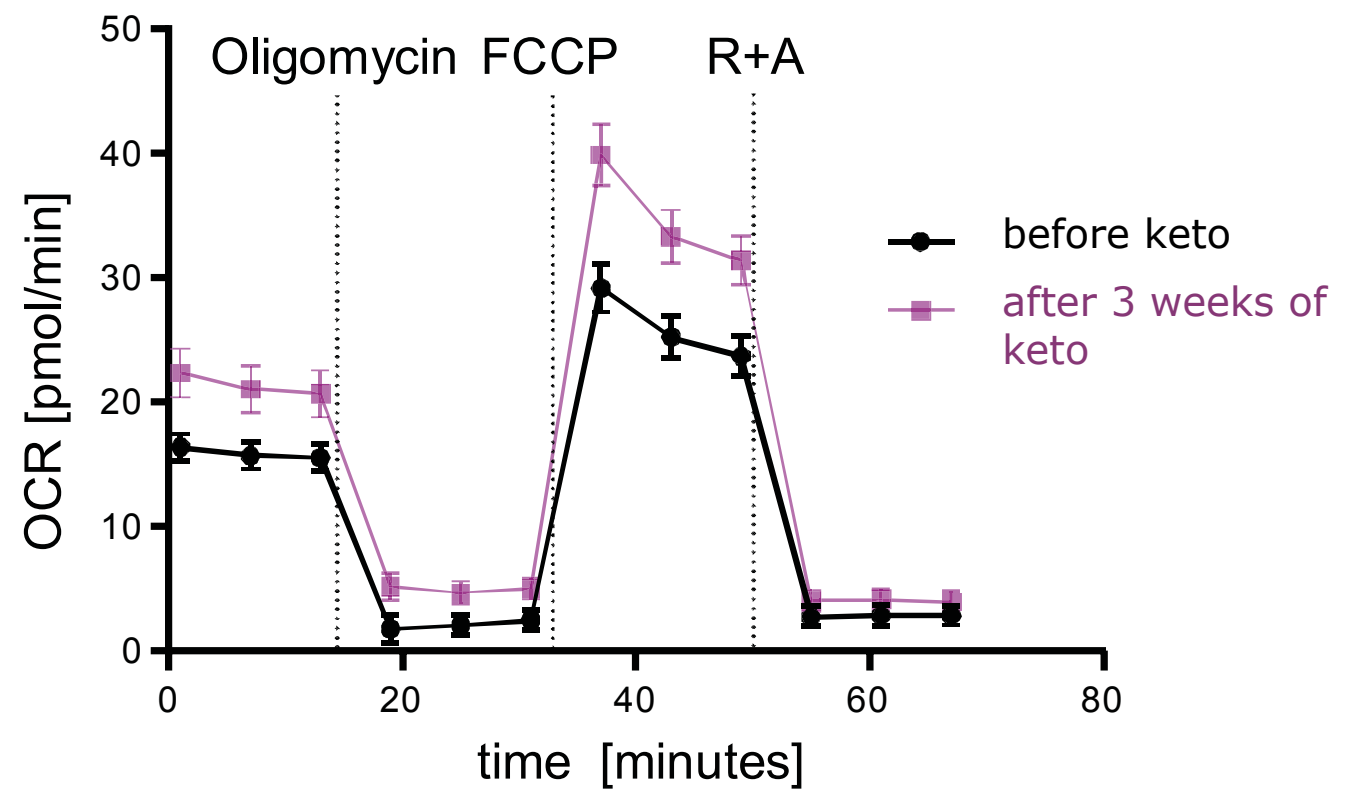
- Metabolism
- General Well-being
- Body Composition
- Immune System

Improved adaptive immune response

Reduced unspecific inflammation






Improved mitochondrial metabolism



Article

SOURCE
DATATRANSPARENT
PROCESSOPEN
ACCESSEMBO
Molecular Medicine

Very-low-carbohydrate diet enhances human T-cell immunity through immunometabolic reprogramming

Simon Hirschberger^{1,2,†} , Gabriele Strauß^{1,2,†}, David Effinger^{1,2}, Xaver Marstaller¹, Alicia Ferstl¹ , Martin B Müller^{1,2}, Tingting Wu¹, Max Hübner^{1,2}, Tim Rahmel³, Hannah Mascolo¹, Nicole Exner⁴, Julia Heß^{5,6}, Friedrich W Kreth¹, Kristian Unger^{5,6} & Simone Kreth^{1,2,*} 

Abstract

Very-low-carbohydrate diet triggers the endogenous production of ketone bodies as alternative energy substrates. There are as yet unproven assumptions that ketone bodies positively affect human immunity. We have investigated this topic in an *in vitro* model using primary human T cells and in an immuno-nutritional intervention study enrolling healthy volunteers. We show that ketone

century (Olshansky *et al*, 2005; Christ & Latz, 2019). It impairs cellular immunity and evokes systemic low-grade inflammation not only by causing obesity but also by direct reprogramming of immune cells toward a proinflammatory phenotype (Hotamisligil *et al*, 1993; Visser *et al*, 1999; Weisberg *et al*, 2003; Mathis, 2013; Guo *et al*, 2015; de Torre-Minguela *et al*, 2017; Dror *et al*, 2017; Christ *et al*, 2018). Nutritional interventions may hold promise as a tool to prevent and even to treat disease. Unfortunately, most recommen-

Effects of a Ketogenic Diet in humans:

- **Body Composition, Metabolism and Performance: Clear Improvements**
- **Unspecific inflammation: Reduced**
- **T cell immunity: Improved**



Sepsis

A world wide problem



50 000 000 cases per year



> 250 000 cases per year



>35 % mortality

Nutritional Therapy in Intensive Care

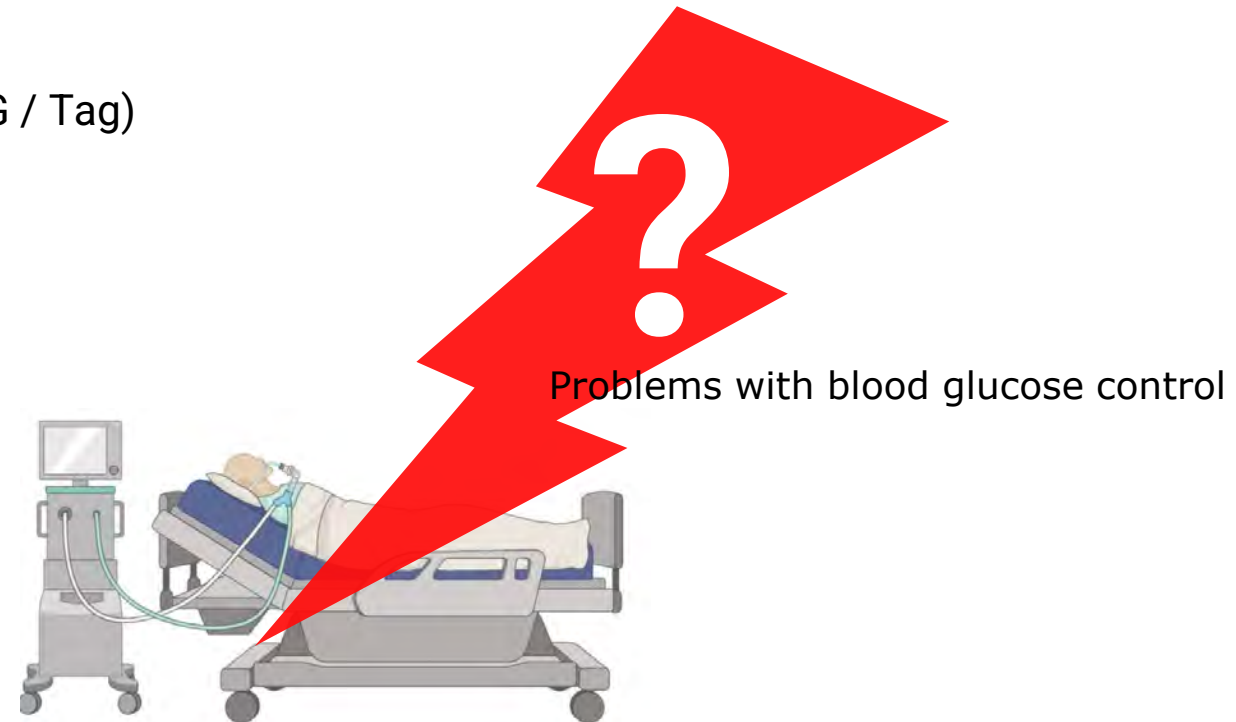
High in Carbohydrates

DGEM (ESPEN) Guidelines

→ Carbohydrates as main energy source (up to 7g/ kg KG / Tag)



Carbohydrate content 45 - 55 %

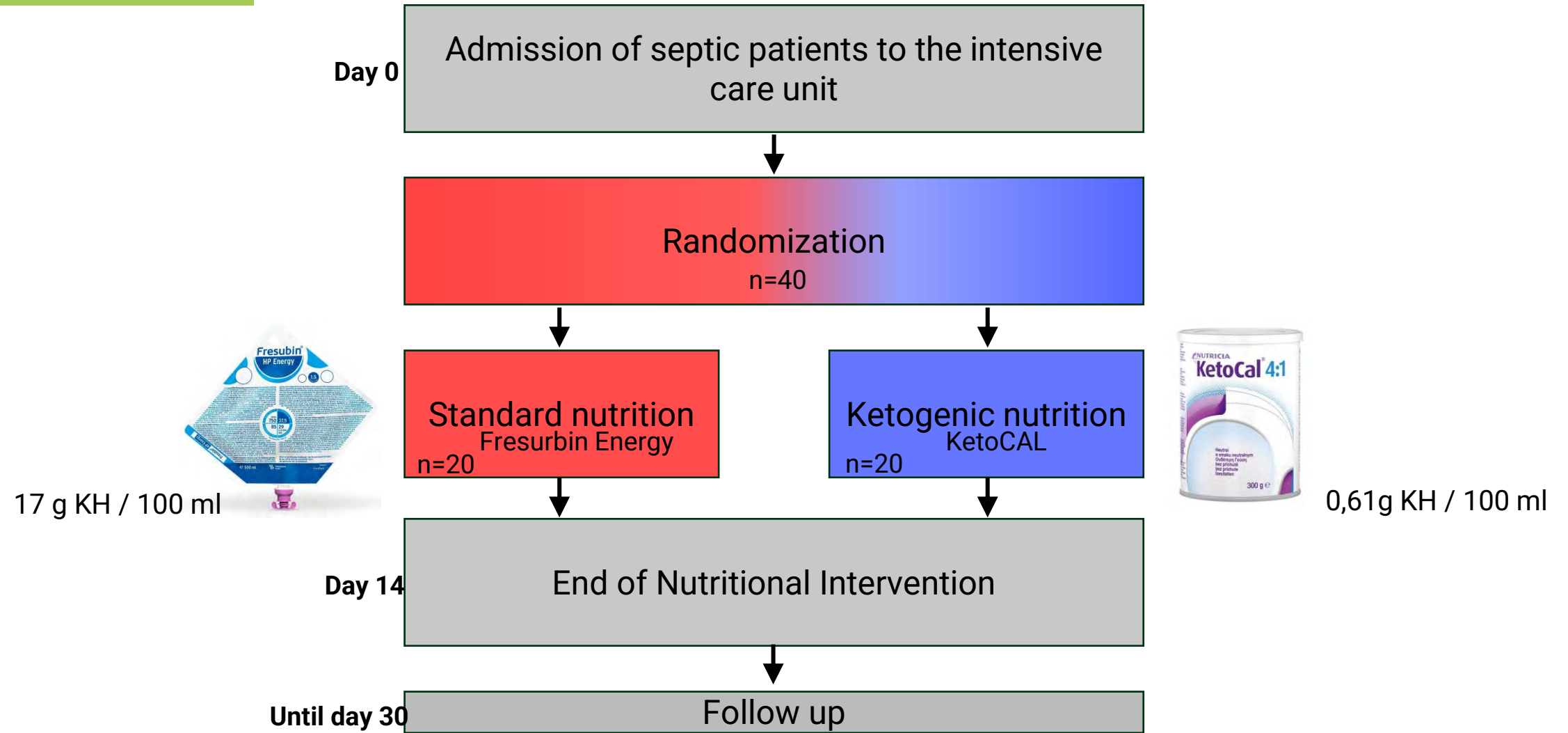


Problems with blood glucose control

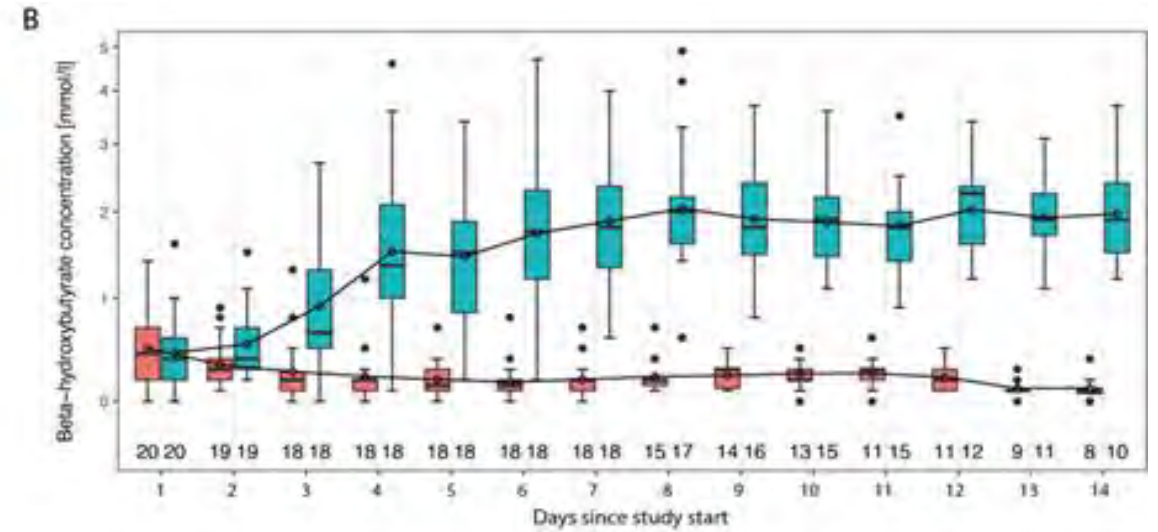
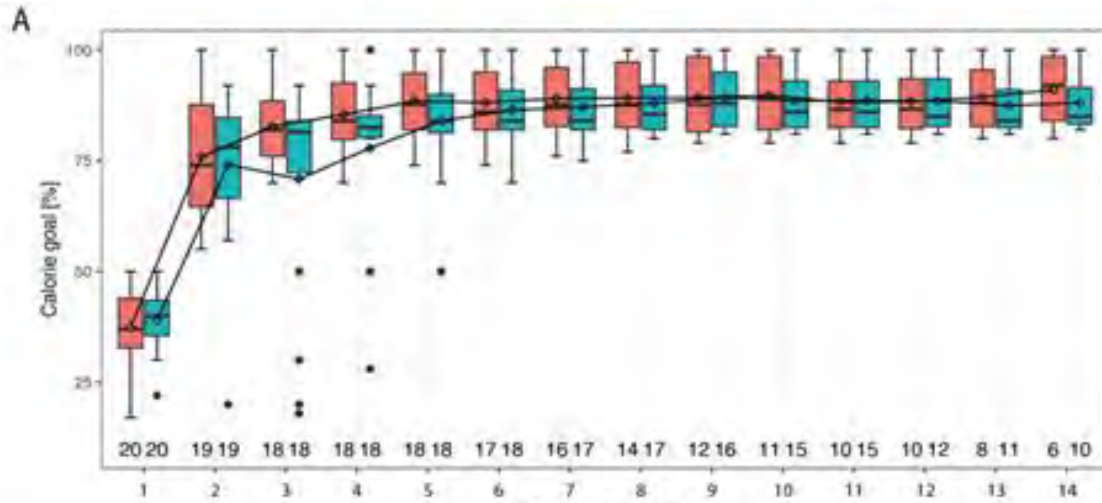
➔ This may aggravate Inflammation !?

Ketogenic Diet in Sepsis Patients

Study Design

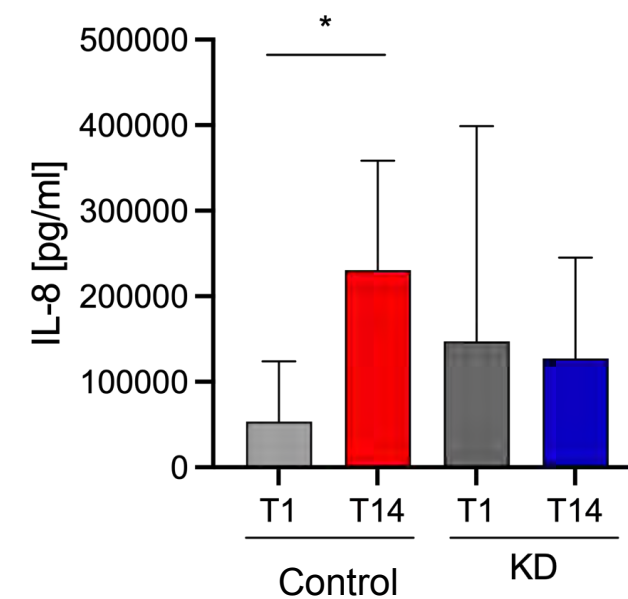
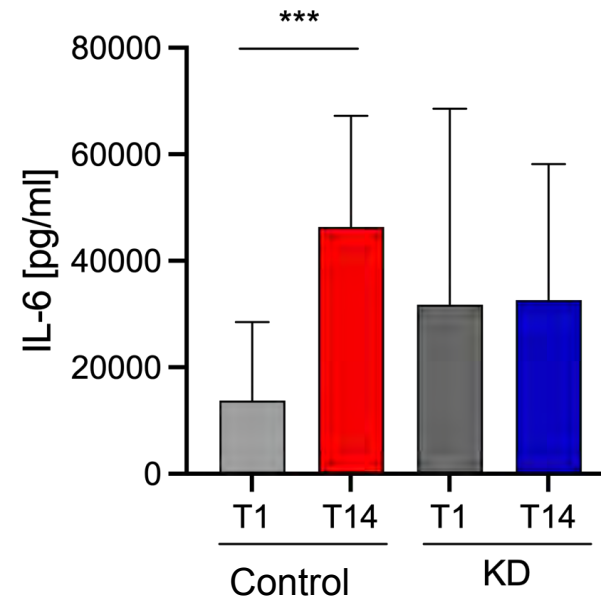
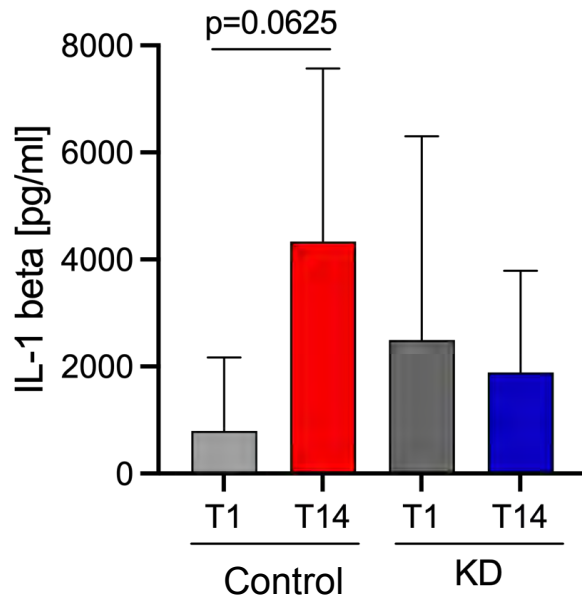


Ketogenic Diet in Sepsis



Ketogenic Diet in Sepsis

Less inflammation



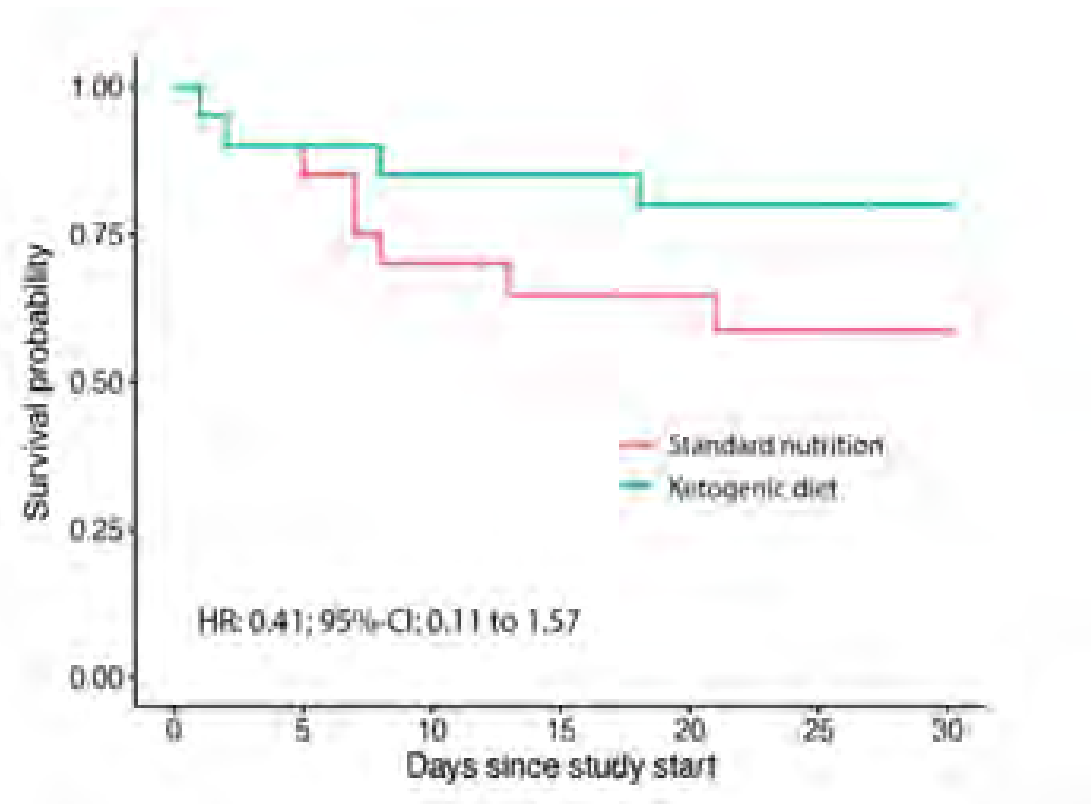
T1 : start
T14 : after 14 days

Ketogenic Diet in Sepsis

Better Outcome

Clinical Outcome Keto:

- More ventilation-free days
- More vasopressor-free days
- More dialysis-free days
- Shorter stay on ICU



SEPSIS

An open-label, randomized controlled trial to assess a ketogenic diet in critically ill patients with sepsis

Tim Rahmel^{1†}, David Effinger^{2,3†}, Thilo Bracht¹, Leonore Griep¹, Björn Koos¹,
Barbara Sitek¹, Max Hübner^{2,3}, Simon Hirschberger^{2,3}, Jale Basten⁴, Nina Timmesfeld⁴,
Michael Adamzik¹, Simone Kreth^{2,3*}

Patients with sepsis experience metabolic and immunologic dysfunction that may be amplified by standard carbohydrate-based nutrition. A ketogenic diet (KD) may offer an immunologically advantageous alternative, although clinical evidence is limited. We conducted a single-center, open-label, randomized controlled trial to assess whether a KD could induce stable ketosis in critically ill patients with sepsis. Secondary outcomes included assessment of feasibility and safety of KD, as well as explorative analysis of clinical and immunological characteristics. Forty critically ill adults were randomized to either a ketogenic or standard high-carbohydrate diet. Stable ketosis was achieved in all KD patients, with significant increases in β -hydroxybutyrate levels compared with controls [mean difference 1.4 millimoles per liter; 95% confidence interval (CI): 1.0 to 1.8; $P < 0.001$]. No major adverse events or harmful metabolic side effects (acidosis, dysglycemia, or dyslipidemia) were observed. After day 4, none of the patients in the KD group required insulin treatment, whereas in the control group, insulin dependency ranged between 35% and 60% ($P = 0.009$). There were no differences in 30-day survival, but ventilation-free [incidence rate ratio (IRR) 1.7; 95% CI: 1.5 to 2.1; $P < 0.001$], vasopressor-free (IRR 1.7; 95% CI: 1.5 to 2.0; $P < 0.001$), dialysis-free (IRR 1.5; 95% CI: 1.3 to 1.8; $P < 0.001$), and intensive care unit-free days (IRR 1.7; 95% CI: 1.4 to 2.1; $P < 0.001$) were higher in the ketogenic group. Next-generation sequencing of CD4⁺/CD8⁺ T cells and protein analyses showed reduced immune dysregulation, with decreased gene expression of T-cell activation and signaling markers and lower pro-inflammatory cytokine secretion. This trial demonstrated the safe induction of a stable ketogenic state in sepsis, warranting larger trials to investigate potential benefits in sepsis-related organ dysfunction.

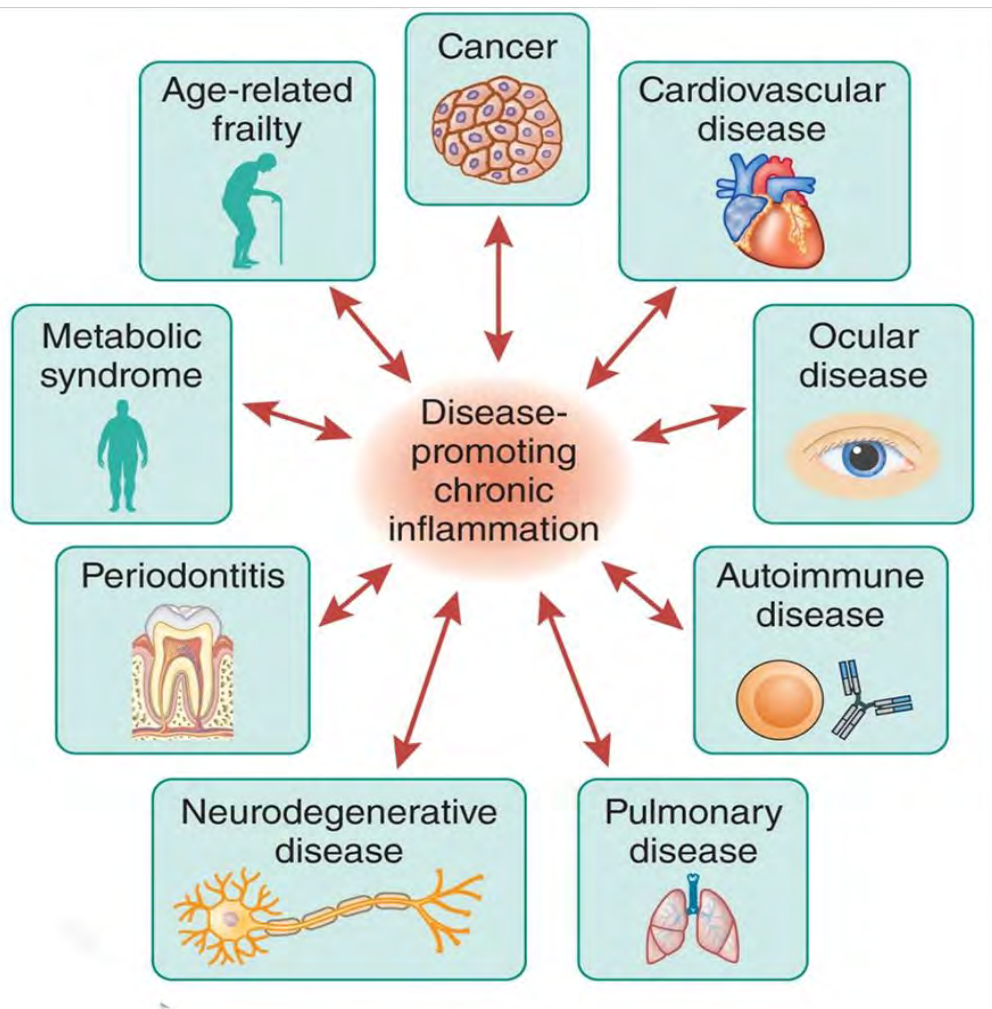


Copyright © 2024 the
Authors; some rights
reserved; exclusive
licensee American
Association for the
Advancement of
Science. No claim to
original U.S.
Government Works

Implementation into a general „Health Concept“?

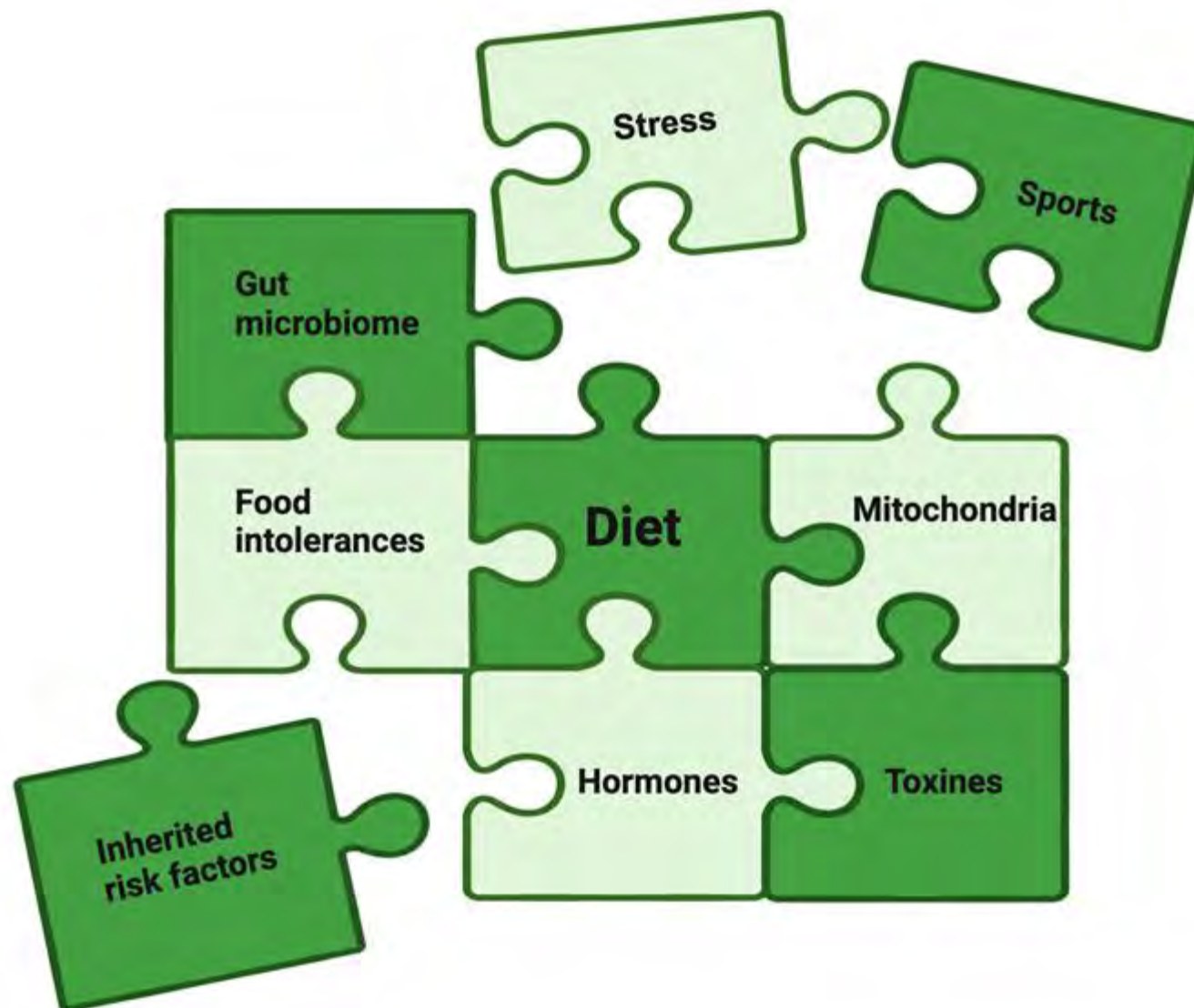
Integrated preventive concept:

Be aware of the beginnings!



- High blood pressure?
 - Deposits in the carotid?
 - Chronic Tiredness?
 - Some overweight?
 - Disc or joint problems?
- ○ ○

Integrated preventive concept:



Second mainstay: Private Practice

Tailoring personalized
Preventive/therapeutic concepts

