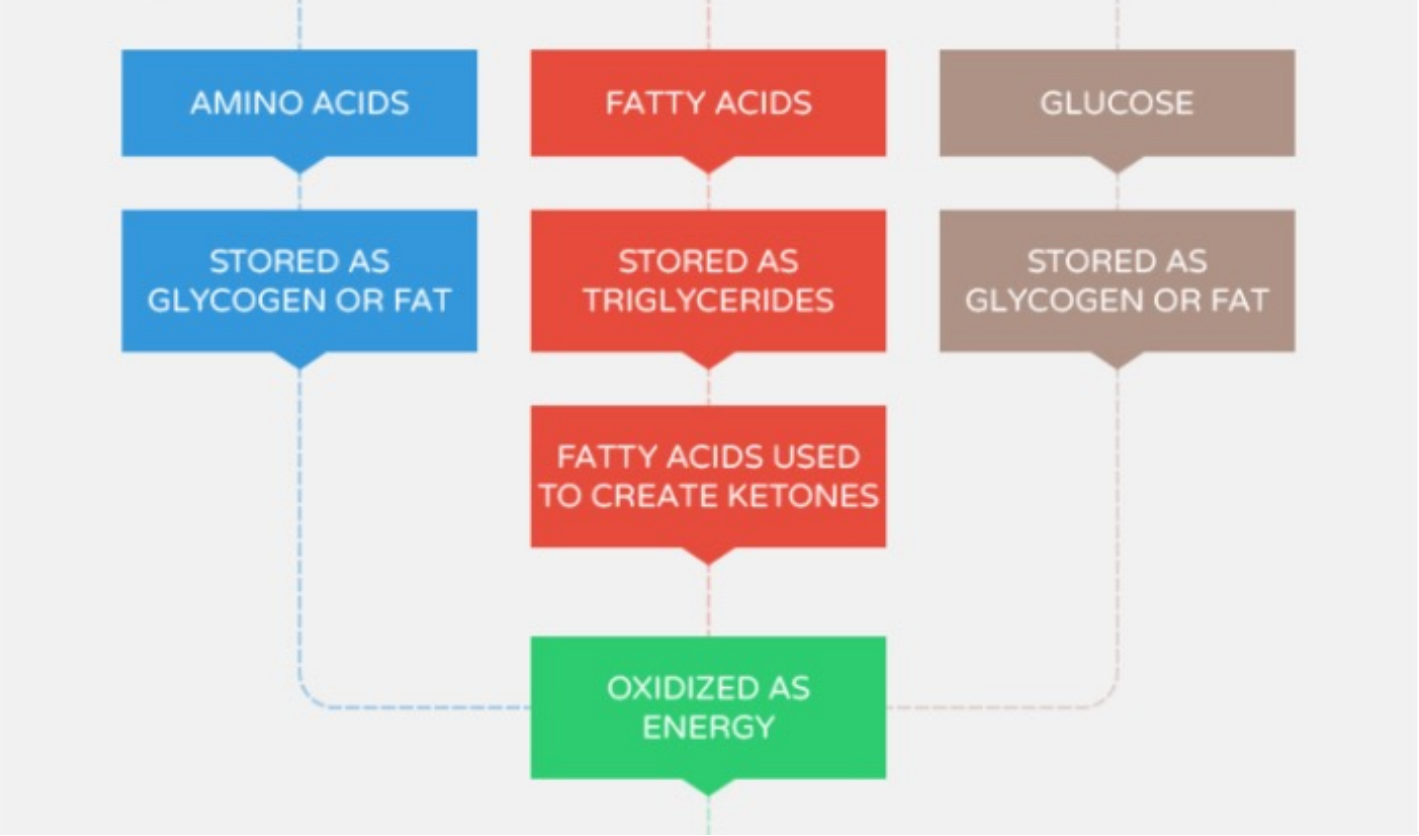
The Practical Science of Fasting

Mindfulness In Biz
正念事業

September 2020

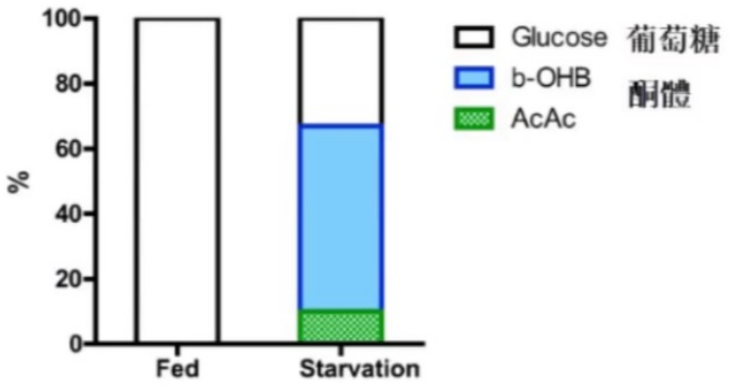
HUMAN METABOLIC PATHWAYS

Our body has different metabolic pathways that it uses to provide energy for our cells. Among the others, Glycolysis (using sugar/glucose for fuel), Gluconeogenesis (turn the amino acids from protein into fuel) and Lipolysis (using fat for fuel through beta-oxidation) are the most well-known metabolic pathways.



FASTING PHYSIOLOGY

- Fasting enables organisms to enter alternative metabolic phases, which rely less on glucose and more on ketone body.
- Both intermittent and periodic fasting result in benefits ranging from prevention to the enhanced treatment of diseases.



Longo & Mattson, Cell Metabolism (2014)

FASTING-RE-FEEDING CYCLES

- Periodic fasting (PF) which refers to a water only or very low calorie period lasting 2 or more days and is separated by the next cycle by at least one week;
- Intermittent fasting (IF), which usually refers to a water only or very low calorie period lasting less than 24 hours and followed by a normal feeding period of one to two days;
- Time-restricted feeding (TRF), in which feeding time is restricted to certain hours of the day, allows the daily fasting period to last >12h, thus imparting pleiotropic benefits in multiple organisms.

FASTING OUTCOMES

Lifespan Extension and Reductions in Age-related Disease

- Periodic fasting (PF) causes the drop in blood glucose pushes cells work harder to utilize other forms of energy, like fatty acids, ketone bodies (fasting physiology); promotes stem cell-dependent regeneration in the immune system, nervous system and pancreas; it will cause a major reduction in the levels of white blood cells but will follow by stem-cell based immune system regeneration upon re-feeding (Cheng et al., 2014)
- Intermittent fasting (IF) causes a decrease in blood glucose, insulin-like growth factor 1 (IGF-1) (Lee et al., 2010) and is accompanied by autophagy (Cuervo et al. 2005; Madeo et al., 2010. In addition to weight loss, IF will also bring along anti-aging benefits
- Time-restricted feeding (TRF) refers to eat breakfast after 8am and finish dinner before 8pm (no eating within 3 to 4 hours of going to sleep). Reducing energy intake on a daily basis may allow the fasting physiology to be triggered sooner and to be sustained for longer periods of time than when consuming standard or excessive amounts of calories. Restricting the timing of food intake to a few hours will trigger the fasting physiology after a few hours of feeding cessation on a daily basis. However, a shorter eating window (of 10 hours or less) can be even more effective for weight loss, but it is much harder to maintain and may increase the risk of side effects, such as developing gallstones and possibly increasing the risk of cardiovascular disease.

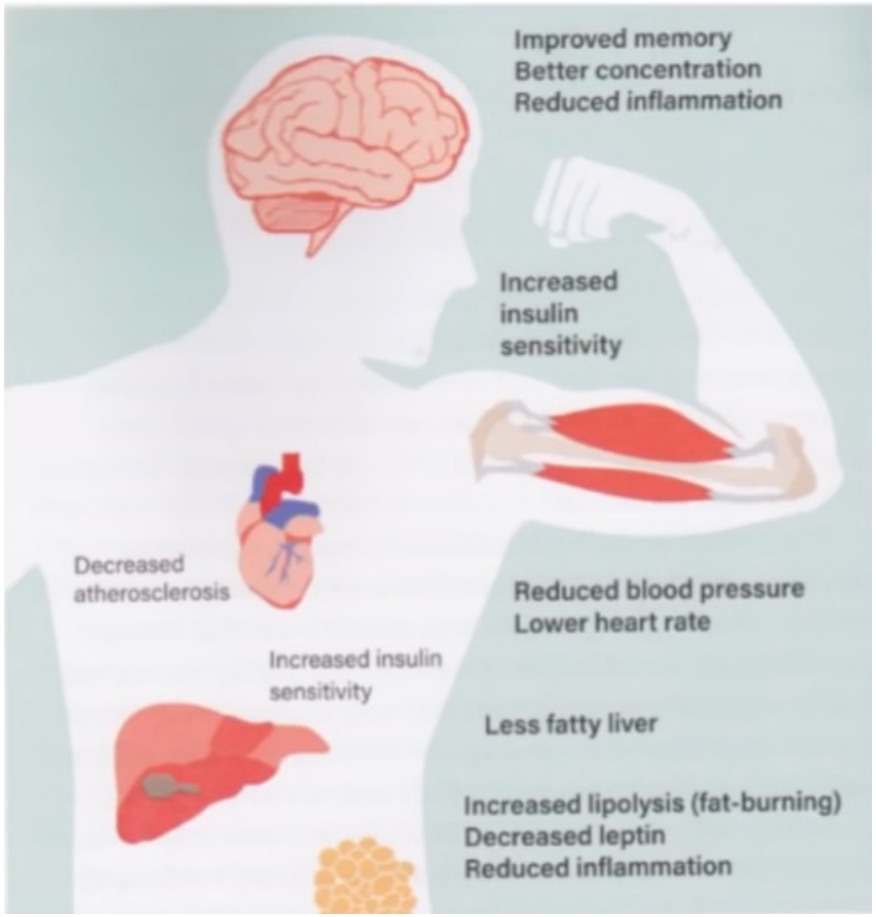
FEEDING

- Low in protein (high-protein diet is associated with increased levels of the pro-aging growth factor IGF-1 before age 65, high IGF-1 levels in the bloodstream with an increase of twofold or more in the incidence of breast, prostate, and other cancer types)
- Largely plant- and fish-based (low-carb diet high in animal fat and protein is associated with increases in overall cancer and cardiovascular disease mortality, with a twofold increase in diabetes)
- Even periodic use of a low-protein , plant-based diet can reduce many markers or risk factors for aging and diseases in ages twenty to seventy
- Rich in complex carbohydrates, olive oil, (intake of saturated animal fats is associated with increase in cancer and diabetes) and nuts
- Deficiencies in certain vitamins such as vitamin D has been associated with an increased risk for diabetes and autoimmune and cardiovascular disease.

FASTING BENEFITS

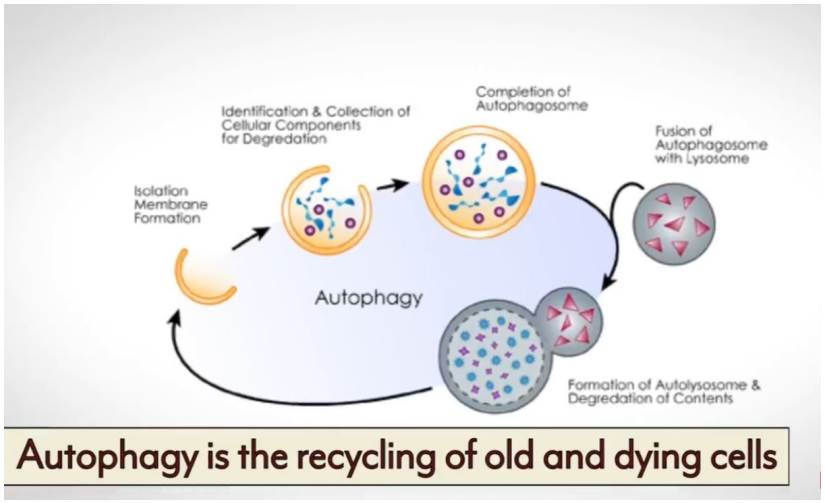
Longevity and Disease Prevention

- Fasting reduce fat accumulation and prevent fatty liver
- Fasting can increase insulin sensitivity
- Fasting can improve metabolic syndrome
- Fasting can increase the number of stem-cells
- Fasting can turn on the autophagy process



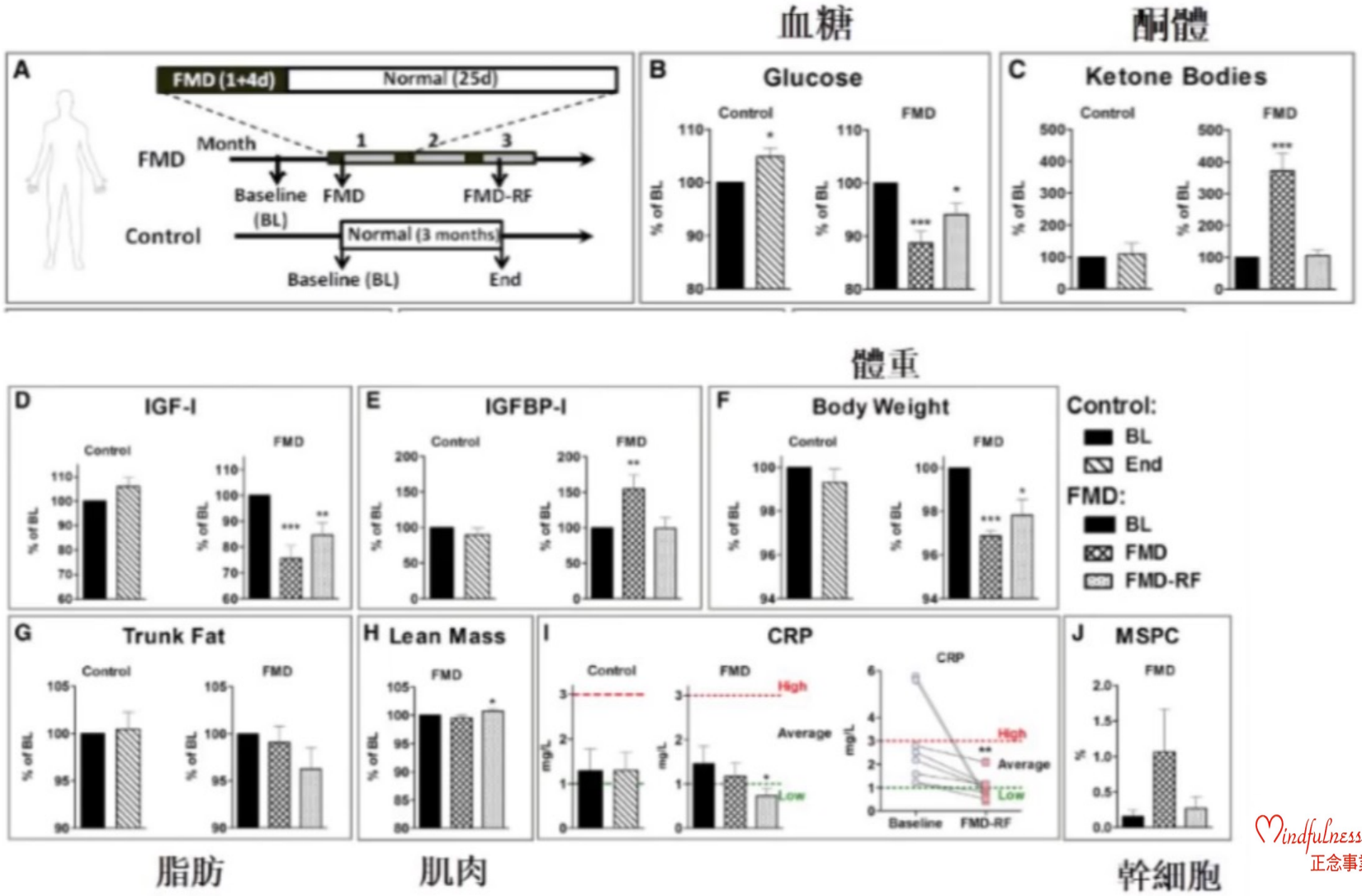
"The Complete Guide to Fasting" by Jason Fung and Jimmy Moore (2016)

FASTING BENEFITS



- Autophagy is the process of 'self-eating' of damaged cells;
- As we age, or even as we're young, proteins and DNA become damaged and they turn over, so we need very healthy proteins and peptides (chains of amino acids) and DNA and RNA. Due to variety of stresses, from oxidative stress to glycated stress, different forms of stresses can damage those proteins and peptides. We therefore need to remove them quickly to get new healthy on in place of those, so we can optimally function in the cell.

FASTING BIOMETRICS

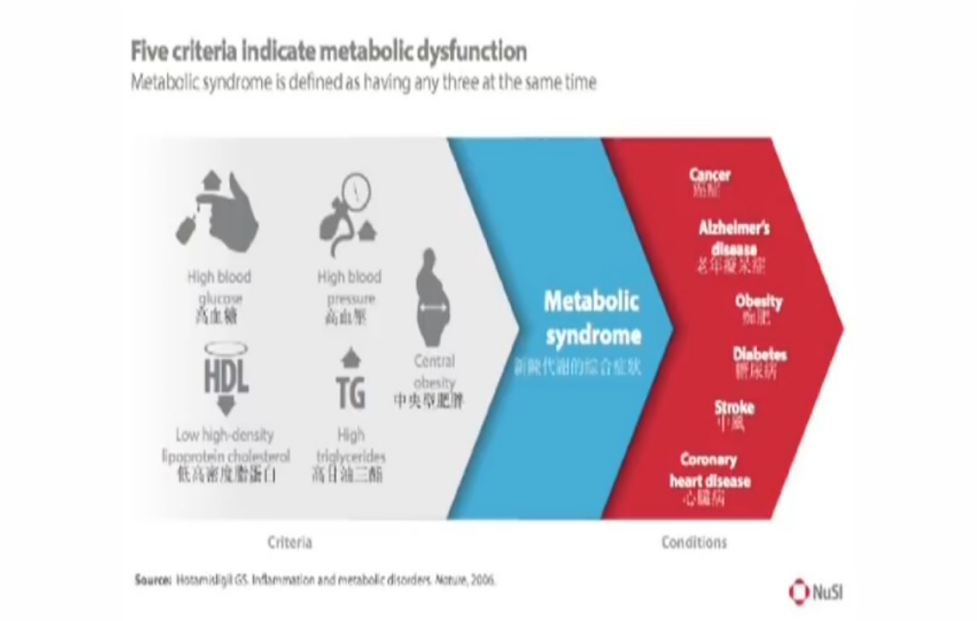


SCIENTIFIC RESEARCH

Metabolic Syndrome and Chronic Diseases

Metabolic syndrome may be diagnosed if one have 3 or more of the following symptoms:

- A waist circumference of 94cm or more in European men, or 90cm in South Asian men; 80cm or more in European and South Asian women
- High triglyceride levels and low levels of HDL in blood
- High blood pressure that's consistently 140/90mmHg or higher
- An inability to control blood sugar levels (insulin resistance)
- An increased risk of developing blood clots, such as DVT (deep vein thrombosis)
- A tendency to develop irritation and swelling of body tissue (inflammation)



Published in final edited form as:
Cell Metab. 2016 June 14; 23(6): 1048–1059. doi:10.1016/j.cmet.2016.06.001.

Fasting, circadian rhythms, and time restricted feeding in healthy lifespan

Valter D. Longo[1,2,*] and **Satchidananda Panda**[3,*]

[1]Longevity Institute and Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089, USA

[2]IFOM, FIRC Institute of Molecular Oncology, Via Adamello, 16, 20139 Milano, Italy

- Modern humans face complex health challenges and solutions. While prevention, vaccination, and treatment for infectious diseases have prolonged lifespan, the presence of artificial light enables human activity throughout the 24h day. This disrupted activity-rest cycle indirectly disrupts the natural daily cycle of feeding and fasting, and facilitates excessive caloric intake. Such chronically disrupted temporal regulation contributes to metabolic diseases but may also accelerate the aging process;

- Treating for metabolic diseases has been challenging, as the traditional pharmacological approach to diseases management may not be sufficient. Long term chronic pharmacological interventions have been particularly successful when the pharmacological molecule is a replacement of an essential biochemical agent, such as insulin (for type 1 diabetes), thyroid hormone, vitamins or minerals which is deficient. These replacement agents often have multiple modes of actions and exert pleiotropic effects;

HHS Public Access
Author manuscript
Cell Metab. Author manuscript; available in PMC 2017 June 14.

Published in final edited form as:
Cell Metab. 2016 June 14; 23(6): 1048–1059. doi:10.1016/j.cmet.2016.06.001.

Fasting, circadian rhythms, and time restricted feeding in healthy lifespan

Valter D. Longo[1,2,*] and **Satchidananda Panda**[3,*]

[1]Longevity Institute and Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089, USA

[2]IFOM, FIRC Institute of Molecular Oncology, Via Adamello, 16, 20139 Milano, Italy

Historical and evolutionary arguments for the safety and potential efficacy of periodic fasting in health and longevity

- The emergence at major university hospitals around the world of complimentary and integrative medicine centers that utilize nutrition, exercise, yoga, and acupuncture to prevent and treat disease is evidence that the medical field is sampling traditional interventions to discover ways of improving and replacing FDA-approved therapies involving peptides, antibodies, and pharmaceuticals (Rakel, 2012).
- Many of standard-of-care therapies are based on the discovery of enzymes, receptors, or other targets that mediate biological effects of interest, followed by the identification of specific drugs or biological that interfere with or enhance the activity of specific targets. Although processes by which the drug target and drug are identified are highly sophisticated, resulting intervention (e.g., the inhibition of cholesterol synthesis by statins or the damage of DNA by chemotherapy drugs) can be viewed as rather unsophisticated strategies. In the case of statins, the inhibition of cholesterol synthesis does not take into account long-term effects of the accumulation of cholesterol precursors or counteracting mechanism by which the human body is capable of synthesizing more cholesterol. In the case of chemotherapy drugs, the obvious collateral damage to non-cancerous cells is clear evidence of the lack of sophistication involved. It is therefore not surprising that years after a drug's initial FDA approval, which is supposedly based on demonstrated efficacy, a wide range of side effects, as well as evidence for limited efficacy, often emerge.

Published in final edited form as:
Cell Metab. 2016 June 14; 23(6): 1048–1059. doi:10.1016/j.cmet.2016.06.001.

Fasting, circadian rhythms, and time restricted feeding in healthy lifespan

Valter D. Longo[1,2,*] and **Satchidananda Panda**[3,*]

[1]Longevity Institute and Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089, USA

[2]IFOM, FIRC Institute of Molecular Oncology, Via Adamello, 16, 20139 Milano, Italy

Historical and evolutionary arguments for the safety and potential efficacy of periodic fasting in health and longevity

- One promising alternative to or complementary to pharmaceutical interventions is to identify dietary and traditional remedies that have been safely utilized for hundreds of years to trigger sophisticated physiological responses resulting from billions of years of evolution. These evolutionary and historical arguments are scientifically meaningless, unless accompanied by (1) insights into their molecular mechanisms of action, (2) extensive and positive cellular and animal data, (3) epidemiological data, and (4) randomized clinical trials.

- Among alternative interventions for the prevention and treatment of chronic metabolic diseases, different forms of fasting have the greatest potential of being integrated into the standard medical care. These range from time restricted feeding (TRF), feeding every other day (alternate day fasting), adopting a reduced calorie regimen twice a week (5:2 fasting).

Published in final edited form as:
Cell Metab. 2016 June 14; 23(6): 1048–1059. doi:10.1016/j.cmet.2016.06.001.

Fasting, circadian rhythms, and time restricted feeding in healthy lifespan

Valter D. Longo[1,2,*] and **Satchidananda Panda**[3,*]

[1]Longevity Institute and Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089, USA

[2]IFOM, FIRC Institute of Molecular Oncology, Via Adamello, 16, 20139 Milano, Italy

Intermittent Fasting (IF) in the prevention and treatment of chronic diseases

- IF can have a wide range of effects on metabolic markers and risk factors or diseases including body fat, blood pressure. In overweight subjects who consumed an approximately 500 kcal but relatively high protein diet for 2 days a week for 6 months, abdominal fat was reduced blood pressure was reduced and insulin sensitivity was increased (Harvie et al., 2011). Similar results were obtained after 2–3 weeks of every other day fasting (Halberg et al., 2005; Heilbronn et al., 2005). A review of findings for all relevant clinical trials assessing both chronic calorie restriction in the 20–50% range (CR) and intermittent fasting, concludes that CR is superior in causing loss of body weight compared to IF, but both interventions have similar effects on the reduction of visceral fat, insulin and insulin resistance (Barnosky et al., 2014).

- IF fasting may also have some effects on inflammatory diseases, since 2 months of alternate day fasting resulted in a significant reduction in inflammatory markers in patients suffering from asthma (Johnson et al., 2007).

HHS Public Access
Author manuscript
Cell Metab. Author manuscript; available in PMC 2017 June 14.

Published in final edited form as:
Cell Metab. 2016 June 14; 23(6): 1048–1059. doi:10.1016/j.cmet.2016.06.001.

Fasting, circadian rhythms, and time restricted feeding in healthy lifespan

Valter D. Longo[1,2,*] and **Satchidananda Panda**[3,*]

[1]Longevity Institute and Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089, USA

[2]IFOM, FIRC Institute of Molecular Oncology, Via Adamello, 16, 20139 Milano, Italy

Periodic Fasting (PF) in the prevention and treatment of chronic diseases

- One of the well-established clinical uses of PF is in the treatment of rheumatoid arthritis (RA). Four different controlled studies have indicated that fasting periods lasting from one to three weeks reduce the symptoms of RA although these effects are reversed by a return to the normal diet unless the PF is followed by a vegetarian diet (Müller et al., 2001).

- PF may also be beneficial in the treatment of hypertension. In a study, 13 days of water only fasting reduced systolic blood pressure below 120 in 82% of subjects with mild hypertension (Goldhamer et al., 2002). PB remained significantly lower after subjects had returned to their normal diet for 6 days. In another study, 10–11 days of fasting decreased systolic blood pressure of hypertensive patients by 37–60 mm, but this study did not follow patients after they returned to their normal diet (Goldhamer et al., 2001).

HHS Public Access
Author manuscript
Cell Metab. Author manuscript; available in PMC 2017 June 14.

Published in final edited form as:
Cell Metab. 2016 June 14; 23(6): 1048–1059. doi:10.1016/j.cmet.2016.06.001.

Fasting, circadian rhythms, and time restricted feeding in healthy lifespan

Valter D. Longo[1,2,*] and **Satchidananda Panda**[3,*]

[1]Longevity Institute and Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089, USA

[2]IFOM, FIRC Institute of Molecular Oncology, Via Adamello, 16, 20139 Milano, Italy

- Both PF and IF have potential applications for inflammatory and cardiovascular diseases, but additional, larger and randomized studies are needed before these strategies can be integrated in the standard of care by physicians.

- If daily (TRF), alternate daily (IF), or periodic fasting (PF) can promote healthy lifespan by exerting pleiotropic effects, restoring a fasting period or switching to a diet that mimics fasting may be an effective treatment strategy for several chronic diseases.

- Several major obstacles may be responsible for the very limited contribution of PF to standard medical practice:
  1. the lack of pre-clinical and clinical data supporting specific and consistent effects of fasting on the prevention and treatment of diseases, and the mechanisms involved,
  2. the safety concerns related to the adoption of water only consumption or the frequently adopted very low calorie diets (approx. 200 kcal) outside of a clinic,
  3. the difficulties associated with compliance to these extreme diets.

- Although, hundreds of thousands of people are likely to undergo some form of PF every year, healthcare professionals strongly recommend that water only or similar fasting interventions be limited to specialized clinics staffed with medical personnel.

Other Scientific Research

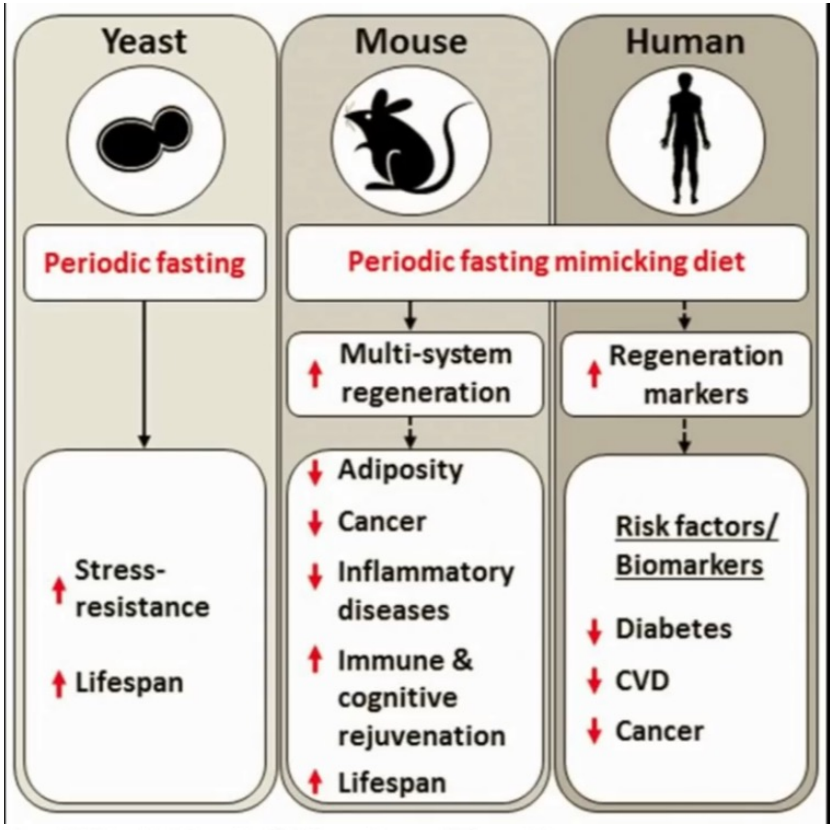
Every one has a doctor in him; we just have to help him in his work. The natural healing force within each one of us is the greatest force in getting well. To eat when you are sick, is to feed your sickness.

~Hippocrates

Medical beneficial effects against…

- Aging (老化)
- Cancer (癌症)
- Cardiovascular diseases/CVD (心血管疾病)
- Neurodegenerative diseases (腦退化)
- Metabolic diseases (代謝疾病)

Other Scientific Research



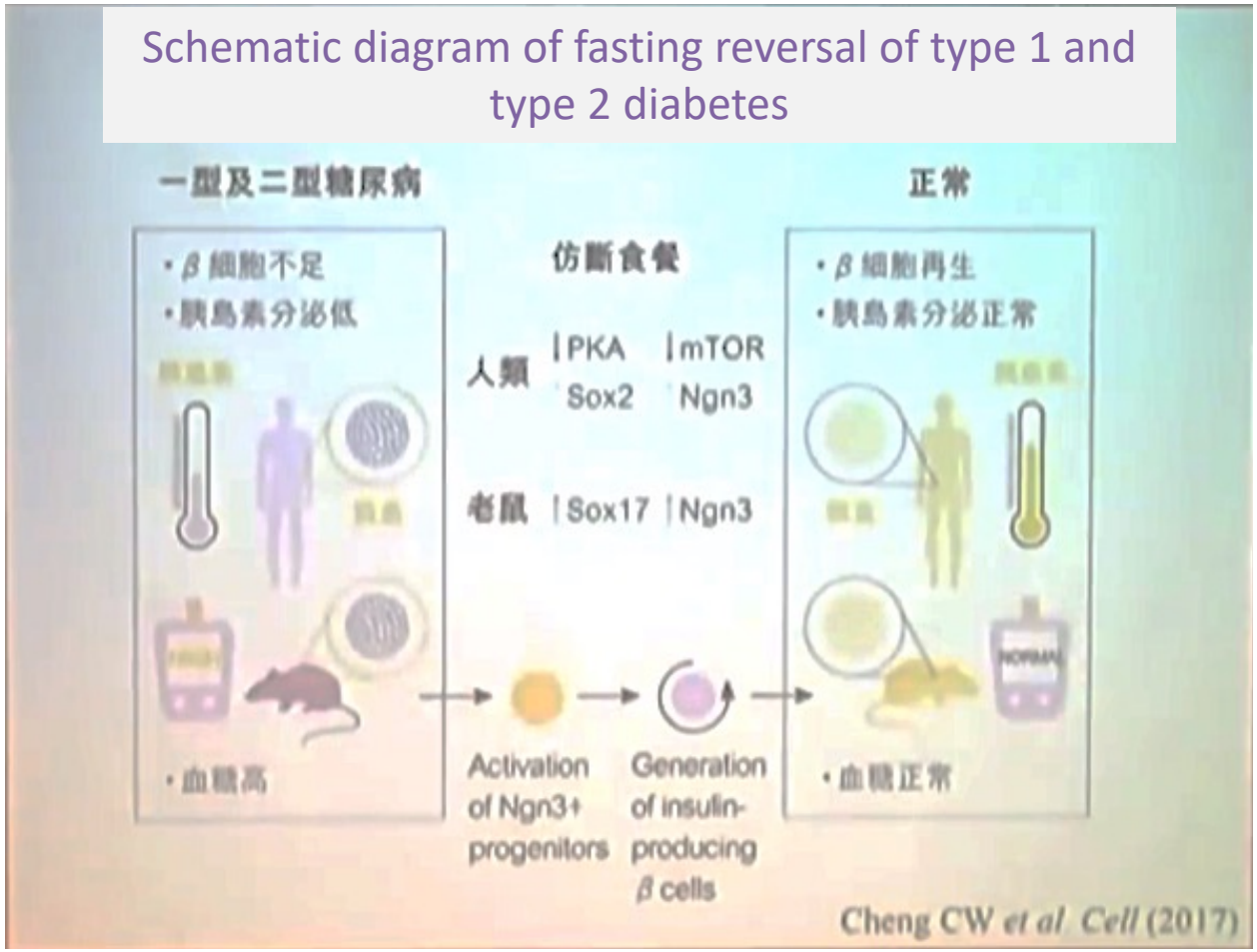
A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan

Sebastian Brandhorst,[1,15] In Young Choi,[1,15] Min Wei,[1] Chia Wei Cheng,[1] Sargis Sedrakyan,[2] Gerardo Navarrete,[1] Louis Dubeau,[3] Li Peng Yap,[4] Ryan Park,[4] Manlio Vinciguerra,[5] Stefano Di Biase,[1] Hamed Mirzaei,[1] Mario G. Mirisola,[6] Patra Childress,[7] Lingyun Ji,[8] Susan Groshen,[8] Fabio Penna,[9] Patrizio Odetti,[10] Laura Perin,[2] Peter S. Conti,[4] Yuji Ikeno,[11] Brian K. Kennedy,[12] Pinchas Cohen,[1] Todd E. Morgan,[1] Tanya B. Dorff,[13] and Valter D. Longo[1,14,*]

Cell Metabolism 22, 86–99, July 7, 2015 ©2015 Elsevier Inc.

Other Scientific Research : Fasting against Diabetes

Schematic diagram of fasting reversal of type 1 and type 2 diabetes



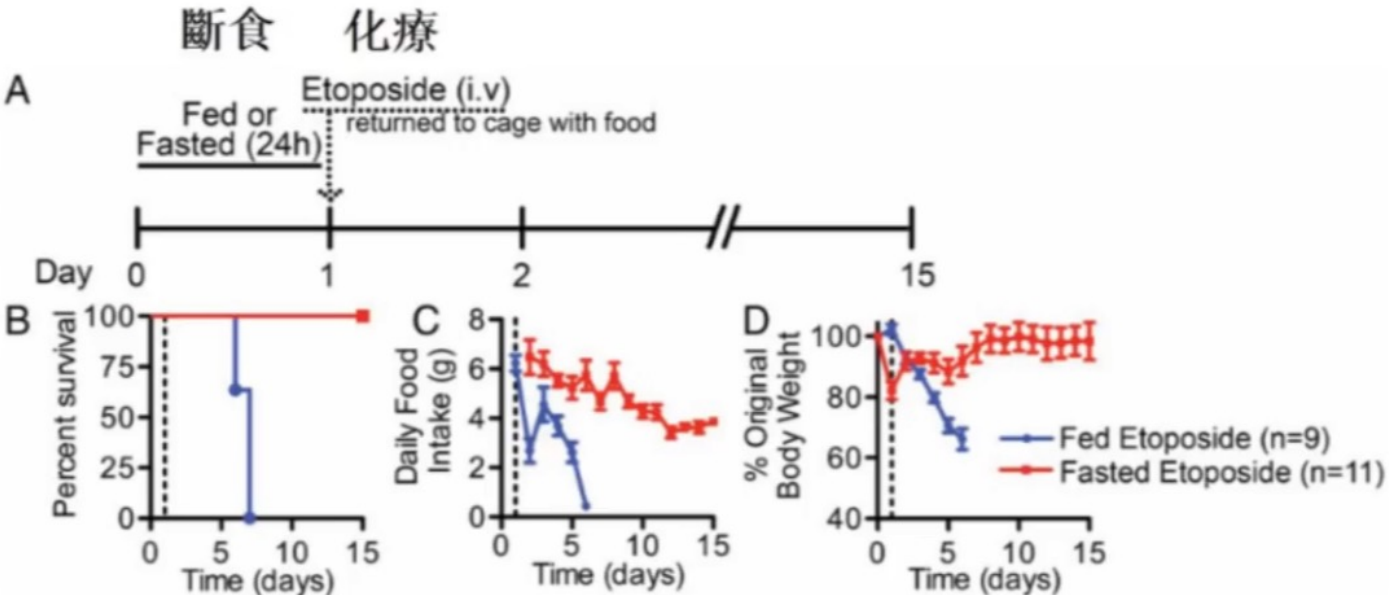
Other Scientific Research : Fasting against Cancer

PNAS

Fasting protects mice from lethal DNA damage by promoting small intestinal epithelial stem cell survival

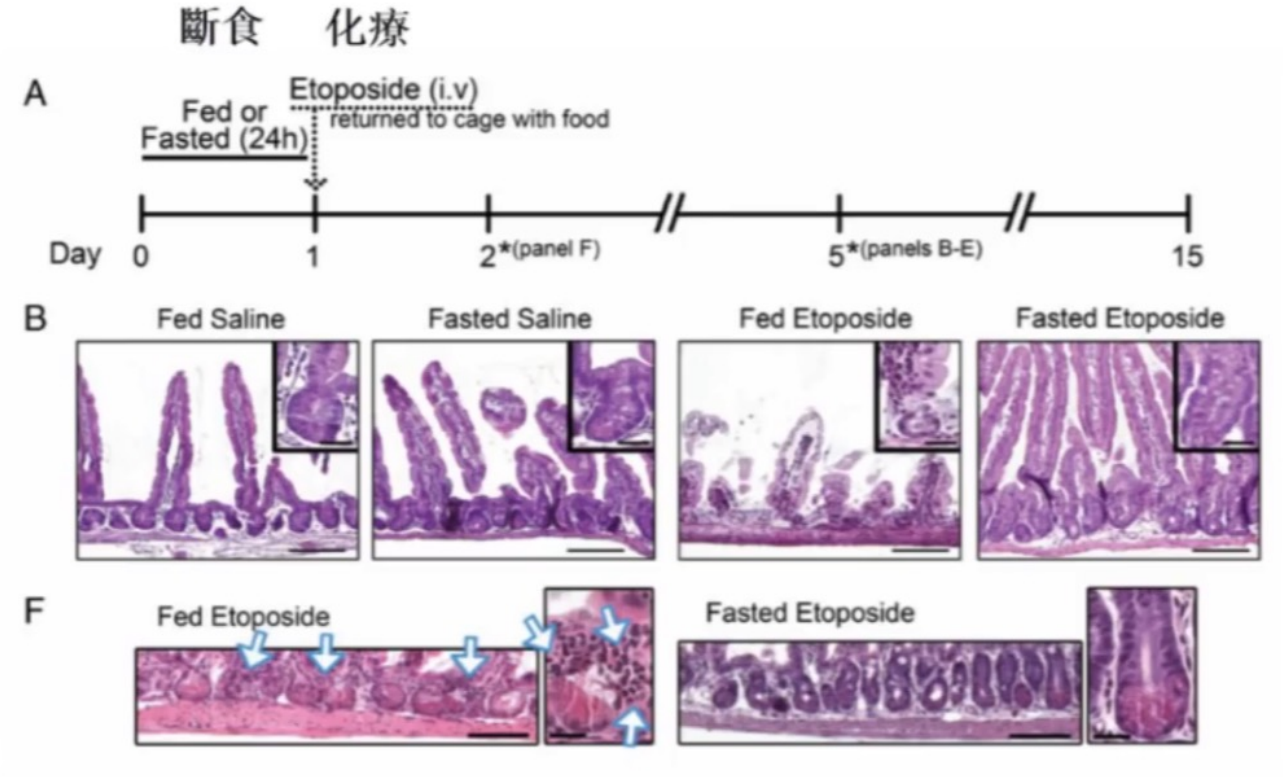
Kelsey L. Tinkum[a,b,1], Kristina M. Stemler[c,1], Lynn S. White[a,b], Andrew J. Loza[d], Sabrina Jeter-Jones[c], Basia M. Michalski[a], Catherine Kuzmicki[a], Robert Pless[e], Thaddeus S. Stappenbeck[f], David Piwnica-Worms[a,b,c,g,2], and Helen Piwnica-Worms[a,c,d,2]

E7148–E7154 | PNAS | Published online December 7, 2015 www.pnas.org/cgi/doi/10.1073/pnas.1509249112



Other Scientific Research : Fasting against Cancer

Fasting can protect intestinal cells from anti-cancer drugs



Other Scientific Research : Fasting against Cancer

Fasting can help the immune system flight cancer

Fasting-Mimicking Diet Reduces HO-1 to Promote T Cell-Mediated Tumor Cytotoxicity

Stefano Di Biase,[1,4] Changhan Lee,[1,4] Sebastian Brandhorst,[1] Brianna Manes,[1] Roberta Buono,[1] Chia-Wei Cheng,[1] Mafalda Cacciottolo,[1] Alejandro Martin-Montalvo,[2] Rafael de Cabo,[2] Min Wei,[1] Todd E. Morgan,[1] and Valter D. Longo[1,3,*]

Cancer Cell *30*, 136–146, July 11, 2016 © 2016 Elsevier Inc.

Caloric Restriction Mimetics Enhance Anticancer Immunosurveillance

Federico Pietrocola,[1,2,3,23] Jonathan Pol,[1,2,3,5,23] Erika Vacchelli,[1,2,3] Shuan Rao,[6] David P. Enot,[1,7] Elisa E. Baracco,[1,2,3,4] Sarah Levesque,[1,2,3,4] Francesca Castoldi,[1,2,3,4,8] Nicolas Jacquelot,[1,4,9,10] Takahiro Yamazaki,[1,4,9,10] Laura Senovilla,[1,2,3,5] Guillermo Marino,[1,2,3] Fernando Aranda,[1,2,3] Sylvère Durand,[1,7] Valentina Sica,[1,2,3,4] Alexis Chery,[1,7] Sylvie Lachkar,[1,2,3,4] Verena Sigl,[6] Norma Bloy,[1,2,3,4] Aitziber Buque,[1,2,3,4] Simonetta Falzoni,[11] Bernhard Ryffel,[12,13] Lionel Apetoh,[14,15,16] Francesco Di Virgilio,[11] Frank Madeo,[17,18] Maria Chiara Maiuri,[1,2,3,4] Laurence Zitvogel,[1,4,9,10] Beth Levine,[19] Josef M. Penninger,[6,24] and Guido Kroemer[1,2,3,5,7,20,21,22,24,*]

Cancer Cell *30*, 147–160, July 11, 2016 © 2016 Elsevier Inc.

Other Scientific Research : Fasting against Cancer

Cell Cycle 9:22, 4474-4476; November 15, 2010; © 2010 Landes Bioscience

Fasting and differential chemotherapy protection in patients

Lizzia Raffaghello,[2,3] Fernando Safdie,[1,3] Giovanna Bianchi,[2] Tanya Dorff,[3] Luigi Fontana[3,4] and Valter D. Longo[1,*]
[1]Andrus Gerontology Center; Dept. of Biological Sciences; and [3]Norris Cancer Center; University of Southern California; Los Angeles, CA USA; [2]Laboratory of Oncology; Giannina Gaslini Institute; Genova, Italy; [3]Division of Geriatrics and Nutritional Science; Washington University in St. Louis; St. Louis, MO USA; [4]Division of Nutrition and Aging; Istituto Superiore di Sanità; Rome, Italy

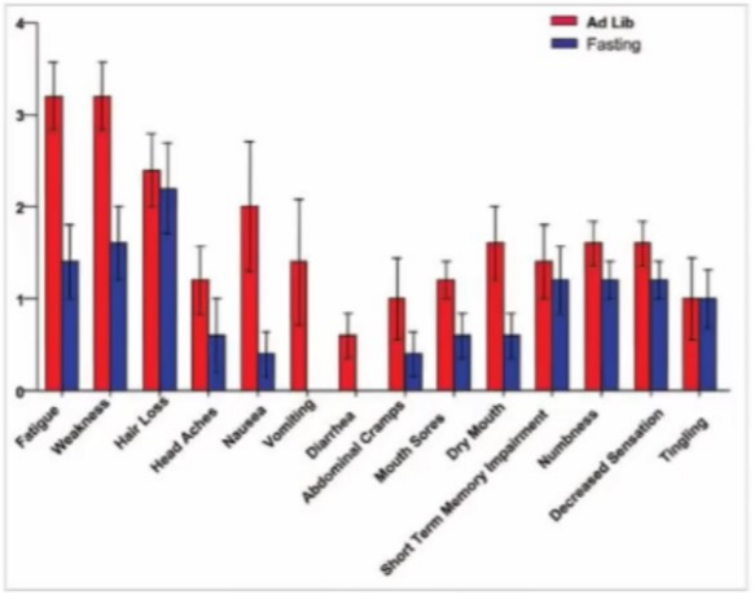


Figure 1. Average self-reported severity of symptoms in patients that have received chemotherapy with or without fasting.

KETO-ADAPTATION

WHAT YOU SHOULD KNOW ABOUT KETO-ADAPTATION

- As carbohydrate levels drop, the body becomes forced to burn stored fat as its primary source of fuel, which can result in often dramatic weight loss;

- The "keto" part refers to ketones, which are water-soluble molecules that the liver makes when metabolizing fats, particularly when carbohydrate intake is low. Ketones can be used for energy by most tissues in your body, including the brain, which can't use unrefined fats as fuel.

WHAT YOU SHOULD KNOW ABOUT KETO-ADAPTATION

- Our body is always using a mix of fat and glucose for energy, but in a non-keto-adapted state, it reaches for glucose first, since only low amounts of ketones are normally generated during fat metabolism and some tissues of the body—for example, the heart—prefer using ketones when they're available. The brain can't use fat, so it depends on glucose when we're in a non-keto-adapted state.

- If glucose is the body's normal go-to source of energy, you may be wondering what happens when it suddenly doesn't have enough to use as its main fuel.

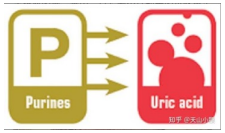
- Keto-adaptation (also sometimes called fat-adaptation) is the process your body goes through on the diet as it changes from using primarily glucose for energy to using primarily fat.

WHEN DOES THE BODY USE KETOGENESIS INSTEAD OF GLUCONEOGENESIS?

- In a review of multiple fasting studies, researchers found that it takes between 18 and 24 hours to deplete glycogen stores and more than 2 days after that for the body to shift into ketosis;

- That's two days without glycogen or ketones for fuel! How is the body fueling itself during that time? With gluconeogenesis;

- In the studies, there was a significant increase in urinary nitrogen loss from day 1 to day 3 of fasting, which was followed by a steady decrease;



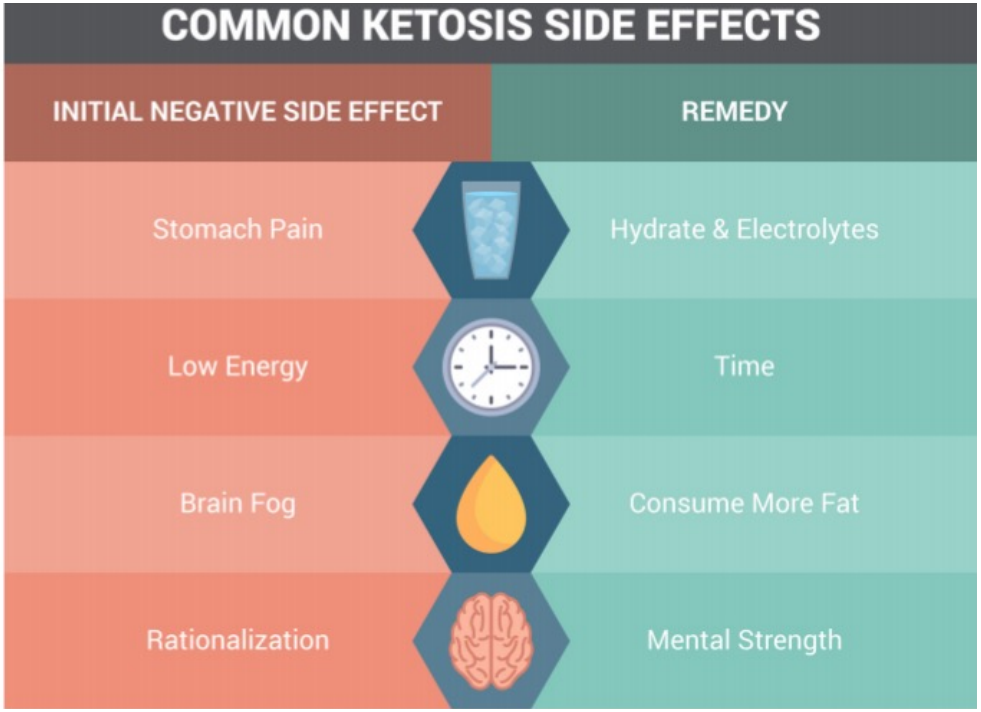
- These findings suggest that the rate at which we use gluconeogenesis decreases after the third day of fasting. Variations occur, however, when we look at the time it takes for different people to shift from gluconeogenesis to ketogenesis as the dominant metabolic pathway.

GETTING TO A KETO-ADAPTIVE STATE

- Once stores of glycogen (the way the body warehouses glucose) become depleted, your brain and other organs begin the process of adapting to using fats and ketones instead of glucose as its main fuel. But reaching ketosis, the state in which fat provides most of the fuel for your body, isn't usually a pleasant experience;

- The extreme carb restriction is often accompanied by adverse side effects. Commonly known as the "keto flu," the transition may cause a period of fatigue, weakness, lightheadedness, "brain fog," headaches, irritability, muscle cramps, and nausea.

GETTING TO A KETO-ADAPTIVE STATE



GETTING TO A KETO-ADAPTIVE STATE

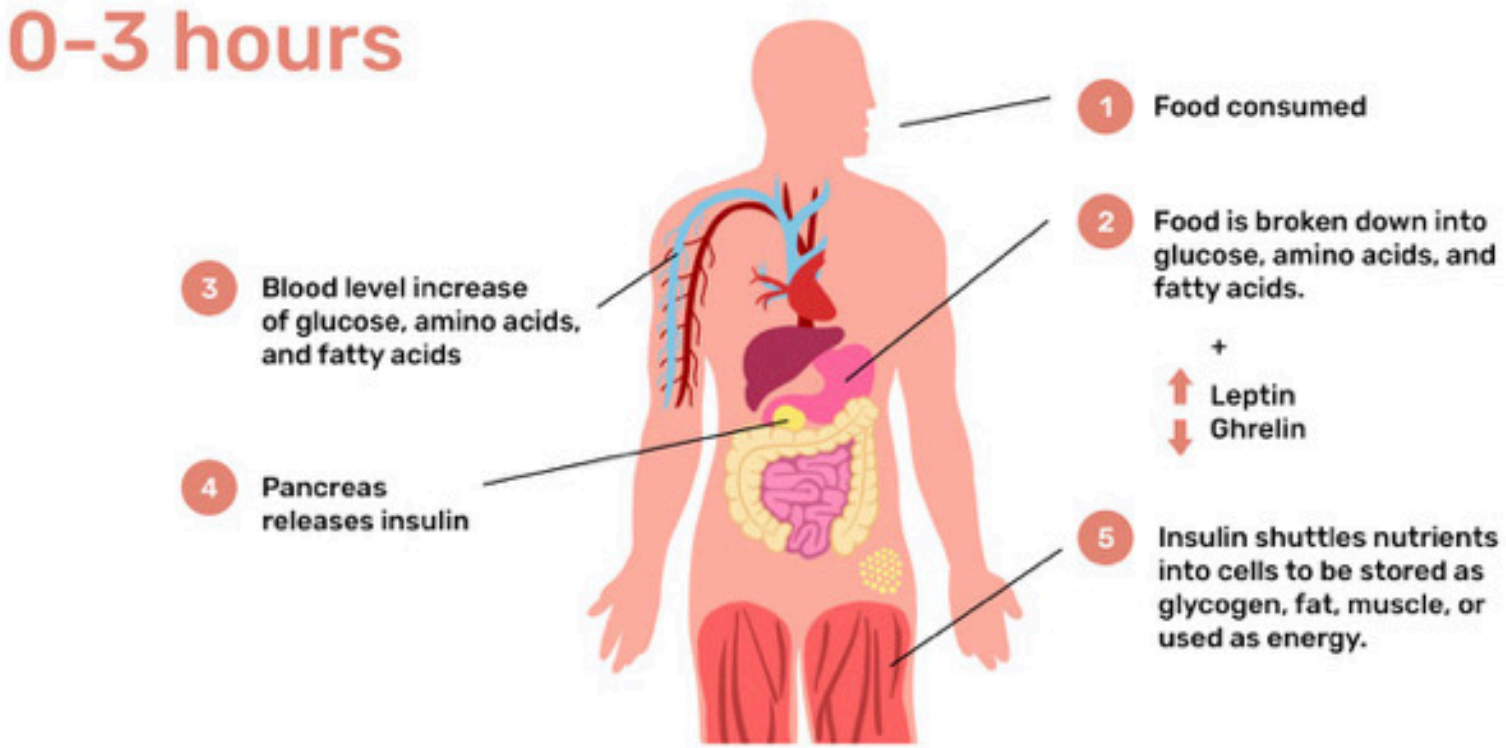
- While the length of time it takes to adapt to a keto diet varies, the process begins after the first few days. Then, after about 3 to 10 days, many low-carbers suddenly start to feel the positive effects of keto-adaptation. They report improved mental concentration and focus and more physical energy as well.

- By the end of the first week (sometimes up to two weeks), the body has usually accomplished the majority of its work in adapting to using fat for energy. By this point, hunger and food cravings are diminished and stamina and vitality increased.

- After this, the body continues to make more subtle changes. For example, it gradually becomes more conserving of protein, so people often crave less protein. Another change that athletes often notice is less lactic acid buildup in their muscles with long training sessions, which translates into less fatigue and soreness. It can take up to 12 weeks for these changes to occur and for you to fully reach ketosis.

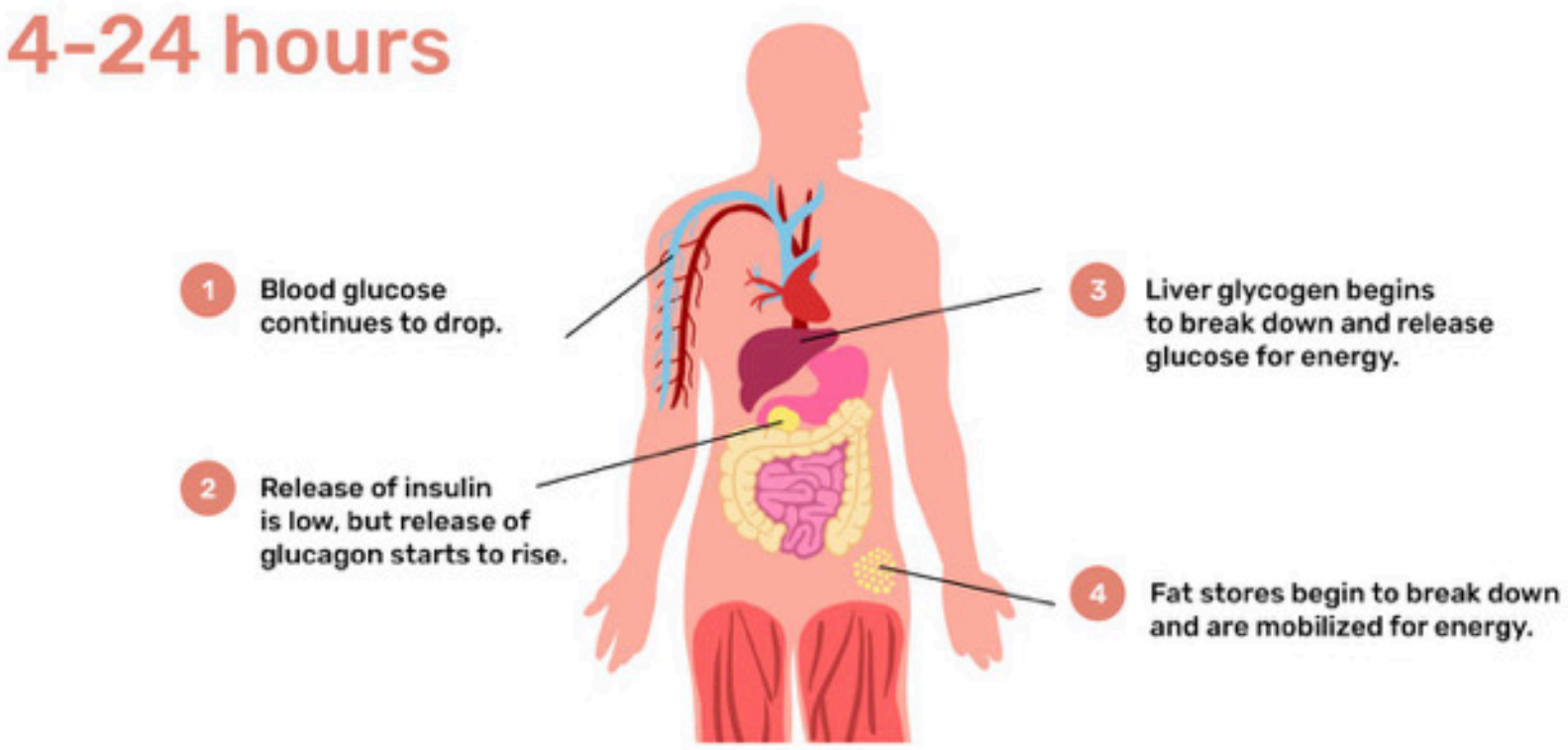
THE PHYSIOLOGY OF FASTING

General Timeline



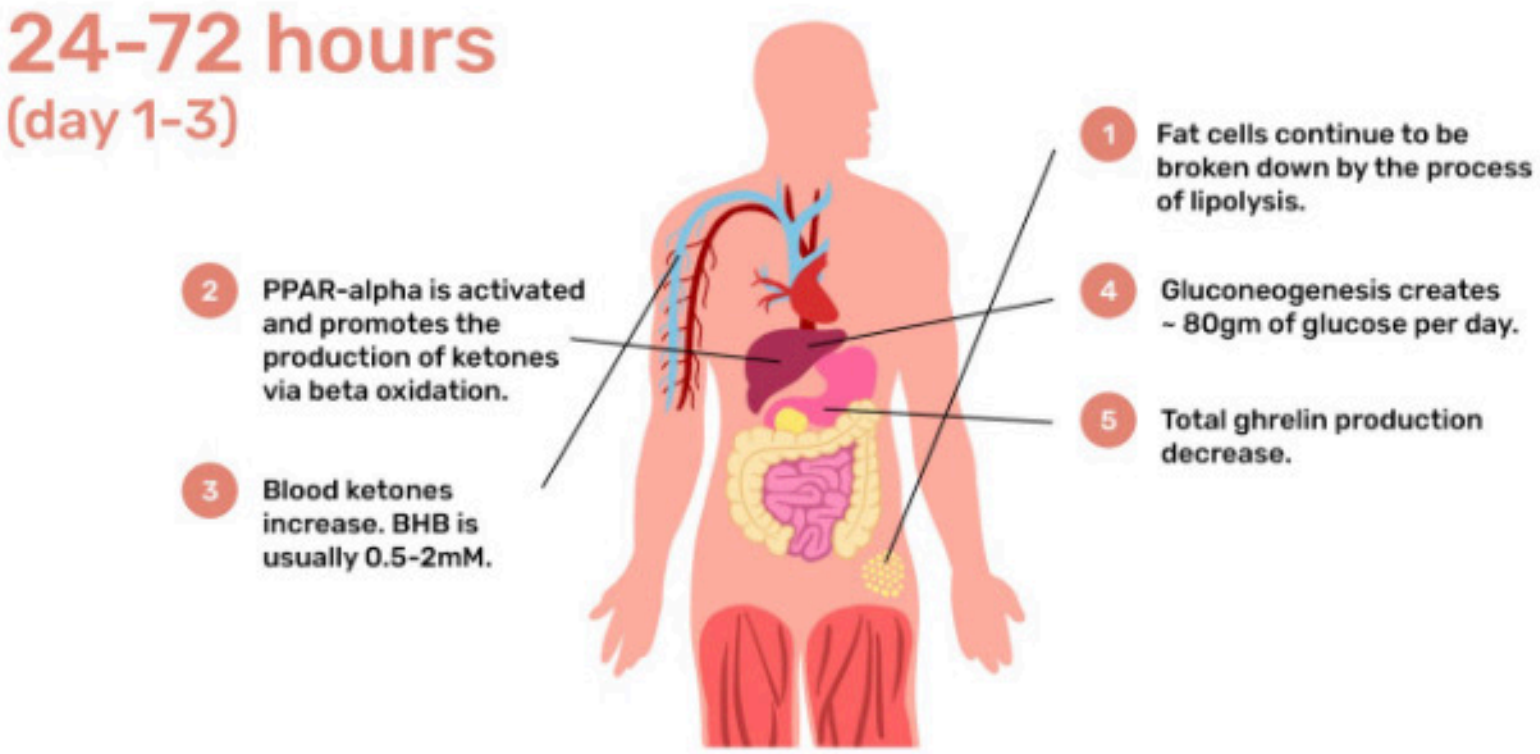
THE PHYSIOLOGY OF FASTING

General Timeline



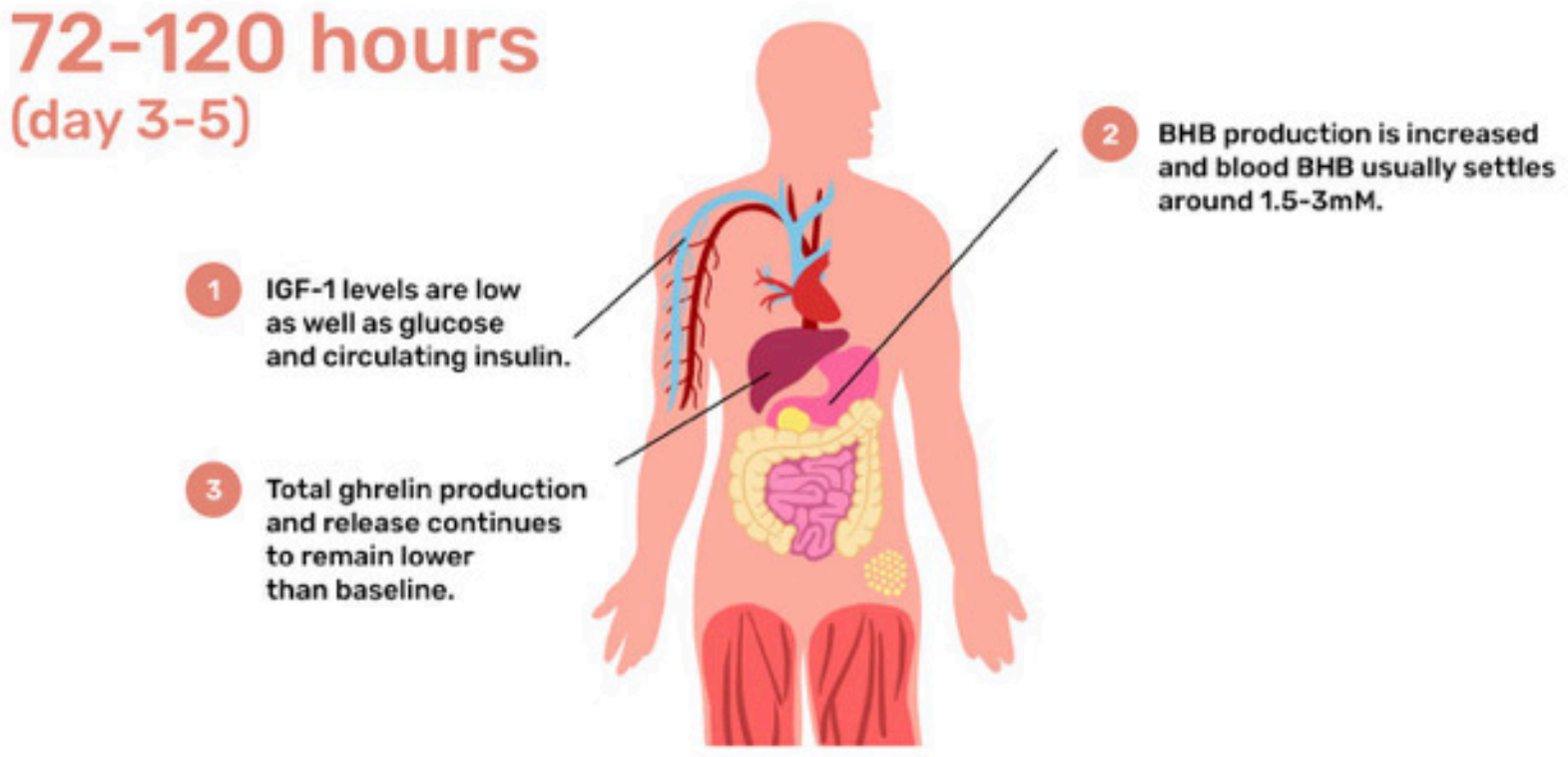
THE PHYSIOLOGY OF FASTING

General Timeline



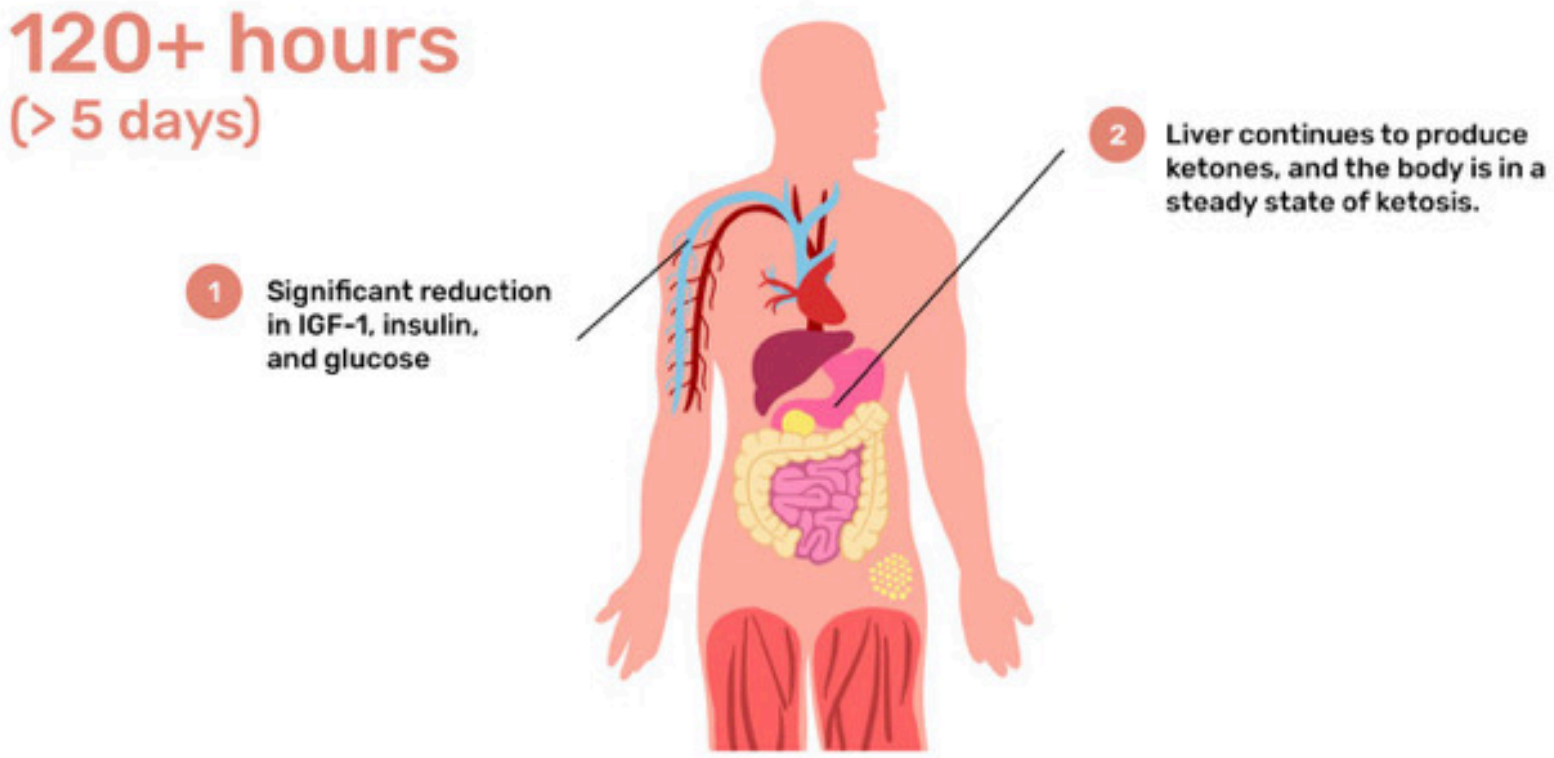
THE PHYSIOLOGY OF FASTING

General Timeline



THE PHYSIOLOGY OF FASTING

General Timeline



FROM GLYCOLYSIS TO GLUCONEOGENESIS TO KETOGENESIS

The path to ketogenesis can be summarized in three stages:

Stage 1 : The postabsorptive phase — 6 to 24 hours of fasting

During this phase, most energy is provided by glycogen.

Stage 2 : The gluconeogenic phase — 2 to 10 days of fasting

During this phase, glycogen is depleted and gluconeogenesis takes over to provide the body with energy. The window of time for this phase is so broad (2 to 10 days) because it depends on who is fasting. If you are a healthy male or obese, it will take longer for you to get to stage 3.

Stage 3 : The protein conservation phase — after 3 to 10 days of fasting

This phase is characterized by a decrease in protein breakdown for energy and an increase in fat and ketone use. Although this phase as described occurring after 10 days of fasting, many people enter this stage after 3 days of fasting.

There you have it — the three stages that everyone goes through before reaching ketosis. Whether we are fasting from carbohydrates (the ketogenic diet or FMD) or fasting from all food, we will go through these stages as well.

“He that eats till he is sick must fast till he is well.”

T. Fuller

Gnomologia; Adagies and Proverbs, 1732.