



## Utilization of Diet Variation to Support Optimal Health

Adult overweight and obesity are major health concerns in the United States. Some of the most prevalent chronic diseases in America have modifiable weight and diet-related risk factors, including type 2 diabetes, heart disease, hypertension, stroke, and some cancers<sup>1</sup>. Although most people understand that weight loss and changes in dietary habits are necessary to improve health outcomes, the majority of the population continues to suffer from chronic disease and increased weight. Nearly 50% of the US population is obese (BMI greater than 30)<sup>2</sup>.

While more research is released daily to find the one “perfect” diet for all, we are failing as a nation with regards to health and wellness. If the average person can lose weight on a diet but soon gains the weight back and feels worse than before, there is a need for a paradigm shift in addressing weight and wellness.

This paper utilizes Dr. Daniel Pompa’s theory to argue that the application of the body’s innate biological systems through diet variation is the missing piece to support lasting health changes<sup>3</sup>. For the purpose of this paper, diet variation is defined as a shift in dietary patterns and intake, whether daily, monthly, or seasonally.

### **A nation of overweight and overwhelm.**

The diet industry is a billion-dollar business that targets those looking for the ideal formula promising quick results with little effort. The weakness of diet culture stems from a focus on short term shifts in eating behaviors, instead of long-term lifestyle and behavior changes. The allure of a quick fix draws in consumers. After starting a diet, most people will experience a positive shift in health outcomes, regardless of the diet, with the removal of processed foods and an increased intake of nutrient-dense items. Unfortunately, this initial success is often short-lived.

<sup>1</sup> “Heart Disease and Stroke.” *Heart Disease and Stroke | Healthy People 2020*, [www.healthypeople.gov/2020/topics-objectives/topic/heart-disease-and-stroke](http://www.healthypeople.gov/2020/topics-objectives/topic/heart-disease-and-stroke).

<sup>2</sup> “Adult Obesity Facts.” *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 27 Feb. 2020, [www.cdc.gov/obesity/data/adult.html](http://www.cdc.gov/obesity/data/adult.html).

<sup>3</sup> Pompa, Daniel. *Beyond Fasting*. Revelation Health, 2019.

While initial weight loss is achievable for many, weight loss maintenance appears to be much more difficult. Research suggests that more than half of those who can lose weight will regain within two years, while 80% will regain within five years<sup>4</sup>. The more often a person attempts weight loss, the harder it is to lose weight each time the weight is lost and regained.

### ***Is there such a thing as THE best diet?***

Studies have shown that when it comes to initial weight loss, there may be more than one effective diet. Many different popular diets have published peer-reviewed research backing their efficacy<sup>5</sup>. While research may suggest that certain diets are better for specific conditions, there is no one perfect diet for every person. Genetics, environment, comorbidities, gender, and stage of life all affect a person's response to diet changes. An example of the role of the individual response is illustrated in the research conducted by scientists out of Germany who found significant variability between participants in glycemic responses to food. More than 800 separate glycemic measurements were taken after ingestion of the same meals, leading the authors to suggest that personalized diets based on individual factors may be a necessary next step for diet prescriptions<sup>6</sup>.

Further, nutrition studies are far from perfect. The utilization of the pharmaceutical testing model when it comes to nutrition and specific nutrients does not always translate well to real life. When a diet is studied, one change to intake shifts the balance of the entire diet. For example – studying the effect of lowering carbohydrates will, in turn, adjust the amount of protein and fat in the diet to make up for the caloric difference. Often, the calories will also decrease. Given diet affects more than one variable, it becomes difficult to say what specific change is the cause for improved health outcomes<sup>7</sup>.

<sup>4</sup> Hall, Kevin D, and Scott Kahan. "Maintenance of Lost Weight and Long-Term Management of Obesity." *The Medical clinics of North America* vol. 102,1 (2018): 183-197.

doi:10.1016/j.mcna.2017.08.012

<sup>5</sup>Michelle R Jospe, Melyssa Roy, Rachel C Brown, Jillian J Haszard, Kim Meredith-Jones, Louise J Fangupo, Hamish Osborne, Elizabeth A Fleming, Rachael W Taylor, Intermittent fasting, Paleolithic, or Mediterranean diets in the real world: exploratory secondary analyses of a weight-loss trial that included choice of diet and exercise, *The American Journal of Clinical Nutrition*, Volume 111, Issue 3, March 2020, Pages 503–

514, <https://doi.org/10.1093/ajcn/nqz330>

<sup>6</sup>Sample, Ian. "Bespoke Diets Based on Gut Microbes Could Help Beat Disease and Obesity." *The Guardian*, Guardian News and Media, 10 June 2015,

[www.theguardian.com/science/2015/jun/10/personalised-diets-diabetes-obesity-heart-disease-microbes-microbiomes](http://www.theguardian.com/science/2015/jun/10/personalised-diets-diabetes-obesity-heart-disease-microbes-microbiomes).

<sup>7</sup> Weaver, Connie M, and Joshua W Miller. "Challenges in conducting clinical nutrition research." *Nutrition reviews* vol. 75,7 (2017): 491-499. doi:10.1093/nutrit/nux026

As a result, people are confused and overwhelmed. The truth may be that there is not merely one diet that is better than the other, but that each person adapts differently based on biology. While certain foods are undoubtedly beneficial for most, a sixty-five-year-old post-menopausal woman will have different needs and hormonal adaptations as compared to a twenty-five-year-old male triathlete.

### **Matching modern eating behaviors with ancestral dietary intake patterns.**

Lasting weight loss and improved health outcomes may be less about the calories a person eats, and more about the quality of the food consumed and the timing of intake. Matching the diet in a manner that takes into consideration our biological history while adjusting for our modern lifestyle may be the answer to lasting change. Studying the body's innate cellular adaptations and using evolutionary biology to support an individual's long-term health is necessary to accomplish this.

The study of evolutionary medicine helps to examine biological changes or adaptations in the body that have developed over time. While humans have obviously experienced many positive adaptations due to micro evolution, other shifts have led to a greater susceptibility of disease, especially those known as diseases of civilization, such as obesity<sup>8</sup>.

Our ancestors lived in a feast versus famine environment, varying the diet seasonally, monthly, and even daily depending on environmental factors. These factors included seasonal availability, temperature, climate changes, and availability of meat. As Dr. Daniel Pompa notes in his book "Beyond Fasting," our ancestors were unknowingly improving their health through these cycles of feast versus famine<sup>9</sup>. A very small population of modern hunter-gatherers continues this pattern, alternating between high protein and fat intake with higher amounts of plant foods and carbohydrates when meat is not available<sup>10</sup>. Research that has examined existing hunter-gatherers in current time has found that this population has reduced cardiovascular risk<sup>11</sup>. While some have argued that our hunter-gatherer ancestors had shorter

<sup>8</sup> Grunspan, Daniel Z et al. "Core principles of evolutionary medicine: A Delphi study." *Evolution, medicine, and public health* vol. 2018,1 13-23. 26 Dec. 2017, doi:10.1093/emph/eox025

<sup>9</sup> Pompa, Daniel. *Beyond Fasting*. Revelation Health, 2019.

<sup>10</sup> Gibbons, Ann, and Matthieu Paley. "The Evolution of Diet." *National Geographic*, [www.nationalgeographic.com/foodfeatures/evolution-of-diet/](http://www.nationalgeographic.com/foodfeatures/evolution-of-diet/).

<sup>11</sup> Kaplan, Hillard et al. "Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study." *Lancet (London, England)* vol. 389,10080 (2017): 1730-1739. doi:10.1016/S0140-6736(17)30752-3

lifespans, more recent research suggests that may not be the case – with average lifespans of 68-78 years<sup>12</sup>.

In our current food system, varying intake of food is beneficial for our health (as will be discussed in more detail below) and is a pattern that some follow naturally. Factors including seasonal shifts based on food availability and cost, meal patterns, and eating outside the home, as well as changes in patterns based on holidays or disease states, are all small shifts in variability<sup>13</sup>. We can extend our definition of variability to those seeking better health by varying an individual's food intake regularly so as not to subscribe to one single "diet" pattern. Variability can also address feelings of deprivation and boredom that are often experienced by dieters, as well as address individual biological response as noted in the glycemic response study above.

### **How can we use the concept of variation in the modern diet?**

In order to adequately address the solutions to the failures of modern diets and diet culture, we need to examine the problems more closely.

#### ***Current Problem: Food overabundance and availability.***

Americans eat too often, and too much. Unlike the feast versus famine lifestyle of our ancestors, the average American lives in a constant state of an overabundance of food. Even those with food insecurity have access to calorically dense yet nutritionally deficient foods<sup>14</sup>. While in the past, our ancestors experienced cycles of famine; we now live in a period of continuous "feast." The current convenient, three meal a day model is a more recent construct of modern lifestyles<sup>15</sup>. It is a lifestyle of too often and too much.

The "thrifty genotype" theory suggests some people have evolved with the ability to convert excess calories to fat to save for times of fasting in order to survive<sup>16</sup>. Without periods of

<sup>12</sup> Gurven, M. and Kaplan, H. (2007), Longevity Among Hunter- Gatherers: A Cross-Cultural Examination. *Population and Development Review*, 33: 321-365. doi:[10.1111/j.1728-4457.2007.00171.x](https://doi.org/10.1111/j.1728-4457.2007.00171.x)

<sup>13</sup> "Diet Variation, Quantification, and Misreporting." *DAPA Measurement Toolkit*, [dapa-toolkit.mrc.ac.uk/diet/introduction/diet-variation-quantification-misreporting](https://dapa-toolkit.mrc.ac.uk/diet/introduction/diet-variation-quantification-misreporting).

<sup>14</sup> Godoy, Maria. "How America's Wealth Gap Shows Up On Our Dinner Plates." *NPR*, NPR, 18 Sept. 2015, [www.npr.org/sections/thesalt/2015/09/18/441143723/people-on-food-stamps-eat-less-nutritious-food-than-everyone-else](http://www.npr.org/sections/thesalt/2015/09/18/441143723/people-on-food-stamps-eat-less-nutritious-food-than-everyone-else).

<sup>15</sup> De Cabo, R., & Mattson, M. P. (2019). *Effects of Intermittent Fasting on Health, Aging, and Disease*. *New England Journal of Medicine*, 381(26), 2541–2551. doi:10.1056/nejmra1905136

<sup>16</sup> Michael J. Wargovich, Joan E. Cunningham, Diet, Individual Responsiveness and Cancer Prevention, *The Journal of Nutrition*, Volume 133, Issue 7, July 2003, Pages 2400S–2403S, <https://doi.org/10.1093/jn/133.7.2400S>

famine, this stored fat becomes a health risk. The average person has access to whatever food they want at any time, but this theory suggests that the body does not recognize this.

Many people are also no longer in touch with hunger cues and eat meals based on the time on a clock versus experiencing real hunger<sup>17</sup>. Eating out of sync with natural biological cues can disrupt circadian rhythms through altered signaling in the body<sup>18</sup>. Cells in the body respond to cues based on our circadian rhythms. Circadian rhythms are the body's natural cycles supporting human metabolism, among other biological activities<sup>19</sup>. Circadian rhythms are influenced by light, the effect on the suprachiasmatic nucleus in the brain, as well as by specific proteins present in most cells in the body. Circadian rhythms help to regulate critical metabolic processes such as fat burning, insulin secretion, and mitochondrial activity. Research suggests that overriding circadian rhythms through alterations in the timing of eating, as with people who work night shifts, but even with those who eat late at night, increases chronic disease risk and insulin resistance and may interrupt normal energy balance<sup>20</sup>. Further, constant snacking, especially later in the evening, may lead to excess belly fat, possibly by resetting some of the body's natural metabolic clocks<sup>21</sup>. The word "breakfast" literally means to break the fasting period from the night before, but this fasting is often not prolonged enough for actual health benefits.

***Addressing modern-day overabundance: Learn from our evolutionary biology to address the timing of eating through fasting.***

The foundation of feast versus famine can be applied to modern health in several ways. It is essential to recognize that eating less often is different from simply eating less food as prescribed on low-calorie diets. A typical reduced-calorie diet for weight loss still allows a person to eat whenever they want and does not take into consideration the health benefits of restricted time eating or fasting.

<sup>17</sup> Bingeman, RDN, CD, Brittany, and Jaqueline Neid-Avila, RDN, CD. "Learning to Listen to Hunger and Fullness Cues." *Utah Extension*, digitalcommons.usu.edu/cgi/viewcontent.cgi?article=2851&context=extension\_curall.

<sup>18</sup> "How Eating Feeds into the Body Clock." *ScienceDaily*, ScienceDaily, 25 Apr. 2019, www.sciencedaily.com/releases/2019/04/190425143607.htm.

<sup>19</sup> Zarrinpar, Amir et al. "Daily Eating Patterns and Their Impact on Health and Disease." *Trends in endocrinology and metabolism: TEM* vol. 27,2 (2016): 69-83. doi:10.1016/j.tem.2015.11.007

<sup>20</sup> Patterson, Ruth E, and Dorothy D Sears. "Metabolic Effects of Intermittent Fasting." *Annual review of nutrition* vol. 37 (2017): 371-393. doi:10.1146/annurev-nutr-071816-064634

<sup>21</sup> Andrew W McHill, Andrew JK Phillips, Charles A Czeisler, Leigh Keating, Karen Yee, Laura K Barger, Marta Garaulet, Frank AJL Scheer, Elizabeth B Klerman, Later circadian timing of food intake is associated with increased body fat, *The American Journal of Clinical Nutrition*, Volume 106, Issue 5, November 2017, Pages 1213–1219, <https://doi.org/10.3945/ajcn.117.161588>

In periods of restricted time eating, the body transitions from glucose as a primary fuel to ketone metabolism. After 12-24 hours, the stored glucose in the liver (known as glycogen) is depleted, and the body uses ketone bodies and free fatty acids for energy<sup>22</sup>. Ketone bodies are a significant source of energy for the body, especially the brain, during periods of fasting<sup>23</sup>. Benefits can even be seen in shorter periods of fasting, known as intermittent fasting. The body enters into initial phases of ketosis on average after 12 hours, with 18 hours being a time of significant ketone formation and fat burning<sup>24</sup>.

Several important health adaptations occur during fasting. Cellular defenses to protect against oxidative stress are activated, as well as the removal of damaged cells, known as autophagy (discussed in more detail below)<sup>25</sup>.

Fasting also supports several essential health benefits, including:

- **Immune health.** Studies have shown that periodic fasting initially causes a drop in white blood cells, with a significant restoration of the immune system once the food is reintroduced. A study examining patients undergoing chemotherapy saw a restoration of previously low white blood cells after periods of fasting<sup>26</sup>. The authors hypothesize that during periods of fasting, the body recycles immune cells that are not being used, explaining the initial drop in white blood cell counts. Stem cells are then activated when food is reintroduced to replenish the recycled cells<sup>27</sup>.

<sup>22</sup> Longo, Valter D, and Mark P Mattson. "Fasting: molecular mechanisms and clinical applications." *Cell metabolism* vol. 19,2 (2014): 181-92. doi:10.1016/j.cmet.2013.12.008

<sup>23</sup> de Cabo, Rafael, and Mark P Mattson. "Effects of Intermittent Fasting on Health, Aging, and Disease." *The New England journal of medicine* vol. 381,26 (2019): 2541-2551. doi:10.1056/NEJMra1905136

<sup>24</sup> Anton, Stephen D et al. "Flipping the Metabolic Switch: Understanding and Applying the Health Benefits of Fasting." *Obesity (Silver Spring, Md.)* vol. 26,2 (2018): 254-268. doi:10.1002/oby.22065

<sup>25</sup> IBID

<sup>26</sup> Cheng, Chia-Wei et al. "Prolonged fasting reduces IGF-1/PKA to promote hematopoietic-stem-cell-based regeneration and reverse immunosuppression." *Cell stem cell* vol. 14,6 (2014): 810-23. doi:10.1016/j.stem.2014.04.014

<sup>27</sup> IBID

- **Longevity.** In yeast and animal models, dietary restriction through fasting increases lifespan<sup>28</sup>. Both human and monkey models also show protection against diseases that occur as a result of age, including diabetes, cancer, and cardiovascular disease<sup>29</sup>.
- **Microbiome adaptations.** Several studies conducted on mice found that time-restricted feeding supports a healthy weight, improves gut bacteria diversity, and supports a healthy intestinal barrier<sup>30</sup>.
- **Metabolic improvements.** Studies have shown that not only can intermittent fasting support weight loss, but it also decreases fasting insulin while improving insulin sensitivity<sup>31</sup>. Improvements in blood pressure, cholesterol, triglycerides, and overall inflammatory markers have also been noted as positive outcomes of intermittent fasting<sup>32</sup>.
- **Brain health.** Caloric restriction through fasting is associated with improvements in cognition and brain health. In a study examining adults with cognitive impairment, memory, and cognition were significantly improved after a 12-month intervention of fasting and caloric restriction<sup>33</sup>.
- **Cancer.** While more research is needed, animal models have shown that intermittent fasting can lower tumor growth in aging rodents, while also improving chemotherapy and radiation sensitivity<sup>34</sup>. An observational study on women with breast cancer found that fasting overnight for more than 13 hours was associated with a reduced risk of breast cancer recurrence<sup>35</sup>.

### ***What are the proposed mechanisms behind health improvements and fasting?***

<sup>28</sup> Fontana, Luigi et al. "Extending healthy life span--from yeast to humans." *Science (New York, N.Y.)* vol. 328,5976 (2010): 321-6. doi:10.1126/science.1172539

<sup>29</sup> Liang, Y., Liu, C., Lu, M. *et al.* Calorie restriction is the most reasonable anti-aging intervention: a meta-analysis of survival curves. *Sci Rep* **8**, 5779 (2018).  
<https://doi.org/10.1038/s41598-018-24146-z>

<sup>30</sup> Zarrinpar A, Chaix A, Yooseph S, Panda S. Diet and feeding pattern affect the diurnal dynamics of the gut microbiome. *Cell Metab.* 2014;20(6):1006–1017. doi:10.1016/j.cmet.2014.11.008

<sup>31</sup> de Cabo, Rafael, and Mark P Mattson. "Effects of Intermittent Fasting on Health, Aging, and Disease." *The New England journal of medicine* vol. 381,26 (2019): 2541-2551.  
 doi:10.1056/NEJMra1905136

<sup>32</sup> IBID

<sup>33</sup> Longo, Valter D, and Mark P Mattson. "Fasting: molecular mechanisms and clinical applications." *Cell metabolism* vol. 19,2 (2014): 181-92. doi:10.1016/j.cmet.2013.12.008

<sup>34</sup> . de Cabo, Rafael, and Mark P Mattson. "Effects of Intermittent Fasting on Health, Aging, and Disease." *The New England journal of medicine* vol. 381,26 (2019): 2541-2551.  
 doi:10.1056/NEJMra1905136

<sup>35</sup> Marinac, Catherine R et al. "Prolonged Nightly Fasting and Breast Cancer Prognosis." *JAMA oncology* vol. 2,8 (2016): 1049-55. doi:10.1001/jamaoncol.2016.0164

Fasting appears to promote hormonal changes that support a reduction in overall cellular inflammation. Fasting is considered a period of stress, similar to periods of famine, as seen with our ancestors. These periods of stress allow the body to use metabolic survival mechanisms. Periods of fasting appear to support the body's ability to stress resilience on a cellular level<sup>36</sup>. During fasting, the body moves out of a period of anabolism and focuses on repair through the removal of damaged cellular debris and mitochondrial support<sup>37</sup>.

The ketone bodies used for fuel in periods of fasting also act as signaling molecules<sup>38</sup>. Ketone bodies also stimulate brain-derived neurotrophic factor (BDNF), which stimulates the growth of new neurons from neural stem cells and can promote the expression of genes for oxidative damage repair<sup>39</sup>.

Perhaps one of the most significant benefits during fasting is autophagy. Autophagy is a process where the body removes damaged or unnecessary cells. Autophagy may help protect the body against the natural effects of aging, and may even protect against neurological diseases such as Parkinson's, Huntington's, and dementia<sup>40</sup>.

Autophagy is regulated by two critical signaling pathways, the mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK). Both of these pathways respond based on the presence or absence of nutrients in the body<sup>41</sup>.

The mTOR pathway signals for many body functions, including cellular growth, division, and protein synthesis<sup>42</sup>. This complicated pathway is upregulated during times of nutrient availability to signal for growth and plays an essential role in glucose and lipid control. Alterations in the mTOR pathway also may be involved in diseases such as cancer, obesity, type

<sup>36</sup> Longo, Valter D, and Mark P Mattson. "Fasting: molecular mechanisms and clinical applications." *Cell metabolism* vol. 19,2 (2014): 181-92. doi:10.1016/j.cmet.2013.12.008

<sup>37</sup> de Cabo, Rafael, and Mark P Mattson. "Effects of Intermittent Fasting on Health, Aging, and Disease." *The New England journal of medicine* vol. 381,26 (2019): 2541-2551. doi:10.1056/NEJMra1905136

<sup>38</sup> Puchalska, Patrycja, and Peter A Crawford. "Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics." *Cell metabolism* vol. 25,2 (2017): 262-284. doi:10.1016/j.cmet.2016.12.022

<sup>39</sup> Mattson, Mark P et al. "Intermittent metabolic switching, neuroplasticity and brain health." *Nature reviews. Neuroscience* vol. 19,2 (2018): 63-80. doi:10.1038/nrn.2017.156

<sup>40</sup> Metaxakis, Athanasios et al. "Autophagy in Age-Associated Neurodegeneration." *Cells* vol. 7,5 37. 5 May. 2018, doi:10.3390/cells7050037

<sup>41</sup> Chen, Xihang et al. "Autophagy in Stem Cell Biology: A Perspective on Stem Cell Self-Renewal and Differentiation." *Stem cells international* vol. 2018 9131397. 21 Jan. 2018, doi:10.1155/2018/9131397

<sup>42</sup> Porta, Camillo et al. "Targeting PI3K/Akt/mTOR Signaling in Cancer." *Frontiers in oncology* vol. 4 64. 14 Apr. 2014, doi:10.3389/fonc.2014.00064



2 diabetes, and neurodegeneration<sup>43</sup>. During periods of fasting, the mTOR pathway is inhibited, while autophagy and fat breakdown are initiated through the upregulation of the AMPK pathway. The AMPK pathway recognizes changes in the availability of glucose supporting fat breakdown and supporting anti-inflammatory signaling pathways<sup>44</sup>.

Once the normal dietary intake is continued, the mTOR pathway can resume but will activate the growth of new, healthy stem cells. This process is known as stem cell self-renewal. Several studies have suggested that this regeneration cannot happen without autophagy<sup>45</sup>. The mTOR pathway plays a vital role in the proliferation of stem cells<sup>46</sup>.

Another important factor, human growth hormone (HGH), increases during the fasted state. HGH is made by the pituitary gland and usually peaks at puberty. Deficiency in adults is associated with increases in body fat, osteopenia, and sarcopenia. HGH works to preserve lean body mass during fasting by utilizing fat stores and preserving lean body mass<sup>47</sup>.

It is important to recognize that while periods of fasting utilize stress adaptations, staying too long in the “famine” phase can lead to the body being overstressed. Thus food and proper intake are equally as important as the fasting itself.

***Addressing modern-day overabundance: Learn from our evolutionary biology to address the quality and quantity of dietary intake.***

While fasting provides extensive health benefits, simply eating in a certain window will not lead to positive outcomes if an individual’s nutrient intake is poor. Diets high in processed and inflammatory foods are far removed from a diet designed to meet our biological needs, especially with consideration of our evolutionary biology as these foods did not exist.

In recent years certain diets have risen in popularity as the answer to our weight loss and health problems, especially low carbohydrate diets based on ancestral health principles. As previously

<sup>43</sup> Laplante, Mathieu, and David M Sabatini. “mTOR signaling in growth control and disease.” *Cell* vol. 149,2 (2012): 274-93. doi:10.1016/j.cell.2012.03.017

<sup>44</sup> Sag, Duygu et al. “Adenosine 5'-monophosphate-activated protein kinase promotes macrophage polarization to an anti-inflammatory functional phenotype.” *Journal of immunology (Baltimore, Md. : 1950)* vol. 181,12 (2008): 8633-41. doi:10.4049/jimmunol.181.12.8633

<sup>45</sup> Kanchan P., Scarth W. A., Katharina S. A. Tighrope act: autophagy in stem cell renewal, differentiation, proliferation, and aging. *Cellular and Molecular Life Sciences*. 2013;70(1):89–103. doi: 10.1007/s00018-012-1032-3.

<sup>46</sup> Meng, Delong et al. “mTOR signaling in stem and progenitor cells.” *Development (Cambridge, England)* vol. 145,1 dev152595. 8 Jan. 2018, doi:10.1242/dev.152595

<sup>47</sup> Ho, K Y et al. “Fasting enhances growth hormone secretion and amplifies the complex rhythms of growth hormone secretion in man.” *The Journal of clinical investigation* vol. 81,4 (1988): 968-75. doi:10.1172/JCI113450

mentioned, diet variation for our ancestors included shifts for seasons and accessibility of food. We can take this history and apply it to several current diet patterns.

While successful dietary patterns may have differing characteristics, if followed correctly, they share several factors with a focus on anti-inflammatory fats, unprocessed food, and reduction of refined carbohydrates.

Two diets that address these characteristics have become especially popular in recent years with important research documenting their benefits:

### ***The Ketogenic diet***

The ketogenic diet restricts carbohydrates while providing fat for the majority of daily calories, in addition to moderate amounts of protein. Initially discovered and used for children with epilepsy, the ketogenic diet relies on a state of ketosis for the body's energy needs<sup>48</sup>. When the body moves into ketosis, levels of ketone bodies increase in the blood.

While the popularity of the diet pattern for reasons beyond epilepsy is relatively new, the ketogenic diet has been documented in research for many health benefits:

- Weight loss<sup>49</sup>
- Decreased inflammation<sup>50</sup>
- Protection against oxidative stress<sup>51</sup>
- Improvements in insulin sensitivity<sup>52</sup>

<sup>48</sup> Martin-McGill KJ, Jackson CF, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. Cochrane Database of Systematic Reviews 2018, Issue 11. Art. No.: CD001903. DOI: 10.1002/14651858.CD001903.pub4

<sup>49</sup> Bueno NB, de Melo IS, de Oliveira SL, et al. Very-low-carbohydrate ketogenic diet v low-fat diet for long-term weight loss: a meta-analysis of randomized controlled trials. 2013. In: Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]. York (UK): Centre for Reviews and Dissemination (UK); 1995-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK138038/>

<sup>50</sup> Veech, Richard L. "The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism." *Prostaglandins, leukotrienes, and essential fatty acids* vol. 70,3 (2004): 309-19. doi:10.1016/j.plefa.2003.09.007

<sup>51</sup> Veech, Richard L. "The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism." *Prostaglandins, leukotrienes, and essential fatty acids* vol. 70,3 (2004): 309-19. doi:10.1016/j.plefa.2003.09.007

<sup>52</sup> IBID

- Neurological health<sup>53</sup>
- Decreased triglycerides<sup>54</sup>
- Metabolic syndrome<sup>55</sup>

In addition to periods of fasting when food was not available, our ancestors would be in periods of ketosis at times when only high-fat foods and minimal starches were available. The adaptation to a high fat, low carbohydrate diet was a survival mechanism so that humans could continue to live until more food was available<sup>56</sup>. In his book *Beyond Fasting*, Dr Pompa states “while in ketosis, the body can utilize fat, instead of glucose, for energy. Ketosis also puts the body into a state of autophagy as described with fasting.”<sup>57</sup>

### ***Are there any downfalls to the ketogenic diet long-term?***

Unlike the modern ketogenic diet, ancestral ketosis occurred in cyclical periods – with intermittent availability of higher carbohydrate starchy tubers. While many experience positive health benefits initially on a ketogenic diet, there are potential downfalls of following it strictly long term.

The ketogenic diet has research supporting its efficacy for improving insulin resistance, yet several mice studies have suggested that the ketogenic diet may increase the risk for type 2 diabetes as a result of hepatic insulin resistance<sup>58</sup>. It is unclear if this adaptation is short- or long-term, but more research is needed.

While some individuals do well in ketosis over a longer period of time, many find increases in fatigue over time, especially for those who follow high-intensity exercise programs. Some who

<sup>53</sup> Gano, Lindsey B et al. “Ketogenic diets, mitochondria, and neurological diseases.” *Journal of lipid research* vol. 55,11 (2014): 2211-28. doi:10.1194/jlr.R048975

<sup>54</sup> Boden, Guenther et al. “Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes.” *Annals of internal medicine* vol. 142,6 (2005): 403-11. doi:10.7326/0003-4819-142-6-200503150-00006

<sup>55</sup> Hyde, Parker N et al. “Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss.” *JCI insight* vol. 4,12 e128308. 20 Jun. 2019, doi:10.1172/jci.insight.128308

<sup>56</sup> Pompa, Daniel. *Beyond Fasting*. Revelation Health, 2019.

<sup>57</sup> Bose, K S, and R H Sarma. “Delineation of the intimate details of the backbone conformation of pyridine nucleotide coenzymes in aqueous solution.” *Biochemical and biophysical research communications* vol. 66,4 (1975): 1173-9. doi:10.1016/0006-291x(75)90482-9

<sup>58</sup> Grandl, G., Straub, L., Rudigier, C., Arnold, M., Wueest, S., Konrad, D. and Wolfrum, C. (2018), Short-term feeding of a ketogenic diet induces more severe hepatic insulin resistance than an obesogenic high-fat diet. *J Physiol*, 596: 4597-4609. doi:[10.1113/JP275173](https://doi.org/10.1113/JP275173)

do not follow the ketogenic diet correctly can also have micronutrient deficiencies<sup>59</sup>. The ketogenic diet may affect men and women differently, as seen in a mouse study where males continued to lose weight over time while females ended up gaining weight<sup>60</sup>. The high-fat content in the diet may also increase estrogen in women, which in turn can suppress the thyroid, further affecting weight loss efforts and hormonal adaptations<sup>61</sup>.

As mentioned, stressing the body to a point can be beneficial, as seen with intermittent fasting, but staying in ketosis too long without carbohydrates may cause longer-term stress on the body that can increase levels of the stress hormone cortisol<sup>62</sup>. Cortisol primes the body to store fat, alters sex hormone levels, and raises blood sugar.

Based on the current evidence, it appears that the ketogenic diet has significant benefits, but cycles of increased carbohydrates may be necessary to achieve the maintenance of these benefits without negative effects.

### ***What about the Paleolithic diet?***

Discussions of eating with an ancestral lens should also include what is known as the modern paleo diet. The paleo diet is based on the hypothesized intake of our paleolithic ancestors. While self-proclaimed paleo experts have various views, the primary dietary pattern focuses on the reduction of processed foods with increases of fruits, vegetables, and well-sourced animal products. Grains, sugar, and dairy are eliminated<sup>63</sup>. The original proponents of paleo diet patterns focused on an increase in plant fibers rather than meat, but some more modern variations use meat as the guiding principle<sup>64</sup>.

<sup>59</sup> Shilpa, Joshi, and Viswanathan Mohan. "Ketogenic diets: Boon or bane?." *The Indian journal of medical research* vol. 148,3 (2018): 251-253. doi:10.4103/ijmr.IJMR\_1666\_18

<sup>60</sup> Sex Differences in the Response of C57BL/6 Mice to Ketogenic Diets  
JESSE COCHRAN, PAUL V. TAUFALLELE, KEVIN D. LIN, YUAN ZHANG, E. DALE ABEL  
*Diabetes* Jul 2018, 67 (Supplement 1) 1884-P; DOI: 10.2337/db18-1884-P

<sup>61</sup> Santin, Ana Paula, and Tania Weber Furlanetto. "Role of estrogen in thyroid function and growth regulation." *Journal of thyroid research* vol. 2011 (2011): 875125.  
doi:10.4061/2011/875125

<sup>62</sup> Stimson, Roland H et al. "Dietary macronutrient content alters cortisol metabolism independently of body weight changes in obese men." *The Journal of clinical endocrinology and metabolism* vol. 92,11 (2007): 4480-4. doi:10.1210/jc.2007-0692

<sup>63</sup> Katz, D L, and S Meller. "Can we say what diet is best for health?." *Annual review of public health* vol. 35 (2014): 83-103. doi:10.1146/annurev-publhealth-032013-182351

<sup>64</sup> Eaton, S B, and M Konner. "Paleolithic nutrition. A consideration of its nature and current implications." *The New England journal of medicine* vol. 312,5 (1985): 283-9.  
doi:10.1056/NEJM198501313120505

There are still questions about what foods were indeed a part of the paleolithic diet<sup>65</sup>. While carbohydrates are not necessarily excluded from the paleo diet, followers often follow a lower carbohydrate diet by cutting out processed foods and grain-based carbohydrates, which tend to be calorically dense.

Health improvements similar to the ketogenic diet have also been studied for the paleo diet, including metabolic improvements<sup>66</sup> and weight loss<sup>67</sup>. However, as with the ketogenic diet, there may be downfalls, including nutrient deficiencies, if not followed correctly<sup>68</sup>. Following the paleolithic diet-long term may negatively affect the gut microbiome and increase trimethylamine-N-oxide (TMAO), a potential risk factor for CVD and atherosclerosis in animals and humans<sup>69</sup>. As grains are a significant source of fiber used for the gut bacteria in the production of short-chain fatty acids, it is essential to ensure the intake of adequate prebiotic fibers through non-grain vegetables.

### **If the research supports these dietary patterns, why do we still have a problem with weight?**

While nutrition research helps us understand the benefits of various diets, it is not always supportive of real life. What may work under controlled conditions may not always translate well to actual dietary patterns, as mentioned previously.

<sup>65</sup> Buckley, Hallie R., and Jane E. Buikstra. "Stone Agers in the Fast Lane? How Bioarchaeologists Can Address the Paleo Diet Myth." *SpringerLink*, Springer, Cham, 1 Jan. 1970, [link.springer.com/chapter/10.1007/978-3-319-93012-1\\_7](https://link.springer.com/chapter/10.1007/978-3-319-93012-1_7).

<sup>66</sup> Eric W Manheimer, Esther J van Zuuren, Zbys Fedorowicz, Hanno Pijl, Paleolithic nutrition for metabolic syndrome: systematic review and meta-analysis, *The American Journal of Clinical Nutrition*, Volume 102, Issue 4, October 2015, Pages 922–932, <https://doi.org/10.3945/ajcn.115.113613>

<sup>67</sup> Obert, J., Pearlman, M., Obert, L. *et al.* Popular Weight Loss Strategies: a Review of Four Weight Loss Techniques. *Curr Gastroenterol Rep* **19**, 61 (2017). <https://doi.org/10.1007/s11894-017-0603-8>

<sup>68</sup> Manousou, S et al. "A Paleolithic-type diet results in iodine deficiency: a 2-year randomized trial in postmenopausal obese women." *European journal of clinical nutrition* vol. 72,1 (2018): 124-129. doi:10.1038/ejcn.2017.134

<sup>69</sup> Genoni, A., Christophersen, C.T., Lo, J. *et al.* Long-term Paleolithic diet is associated with lower resistant starch intake, different gut microbiota composition and increased serum TMAO concentrations. *Eur J Nutr* (2019). <https://doi.org/10.1007/s00394-019-02036-y>

Difficulties with weight loss maintenance is a complex combination of hormonal, environmental, and psychological factors<sup>70</sup>. There is also a risk of staying in the “famine” period too long, whether it is from fasting or simply restricting certain macronutrients. In his book, Dr. Pompa notes that short term stress and adaptation will lead to positive benefits in the body. However, longer-term stress will likely counteract any benefits to the diet and potentially lead to inflammation and disease<sup>71</sup>. Most of the research does not examine long term effects that occur over time as the body adapts. Adaptation is based on evolution, too, as the body is designed to respond to diet stress overtime through biological changes in order to survive. It is clear that cutting back on portions does not work long term for the average person<sup>72</sup>. As the body responds to caloric deprivation or significant reduction of a single nutrient, it will fall into survival mechanisms by decreasing metabolic rate and increasing hunger cues<sup>73</sup>.

Adherence can also be difficult for some people if the diet feels too restrictive. Moreover, what happens to the body when it adapts to the new way of eating, and an individual reaches the dreaded plateau, gains the weight back, and stops experiencing health benefits<sup>74</sup>? Weight loss stops. Adaptation takes over, and as mentioned, over time, new health issues may emerge for some people.

### **The solution: Combine health-promoting dietary patterns with research-based fasting strategies to support dietary variation.**

If one is modeling eating behavior after ancestral patterns, then it does not make sense to follow a diet without cycles of change as they experienced. Therefore, a combination of fasting with cycles of health-supportive diets, such as the ketogenic diet, might be the next game-changer for long-term health.

<sup>70</sup> Greenway, F L. “Physiological adaptations to weight loss and factors favouring weight regain.” *International journal of obesity (2005)* vol. 39,8 (2015): 1188-96.

doi:10.1038/ijo.2015.59

<sup>71</sup> Pompa, Daniel. *Beyond Fasting*. Revelation Health, 2019.

<sup>72</sup> Harry R Kissileff, John C Thornton, Migdalia I Torres, Katherine Pavlovich, Laurel S Mayer, Vamsi Kalari, Rudolph L Leibel, Michael Rosenbaum, Leptin reverses declines in satiation in weight-reduced obese humans, *The American Journal of Clinical Nutrition*, Volume 95, Issue 2, February 2012, Pages 309–317, <https://doi.org/10.3945/ajcn.111.012385>

<sup>73</sup> Hall, K.D. (2018), Metabolic Adaptations to Weight Loss. *Obesity*, 26: 790-791.

doi:[10.1002/oby.22189](https://doi.org/10.1002/oby.22189)

<sup>74</sup> Santos, I et al. “Prevalence of personal weight control attempts in adults: a systematic review and meta-analysis.” *Obesity reviews : an official journal of the International Association for the Study of Obesity* vol. 18,1 (2017): 32-50. doi:10.1111/obr.12466

Diets fail for a variety of reasons, as mentioned. Instead of fighting against the body's biology and the human psychological experience, embracing the body's adaptations in combination with addressing psychological barriers can be used to support long-term changes.

Athletes have used diet variation to their benefit for years cycling intake of macronutrients when needed for specific events and decreasing to allow for supportive healing<sup>75</sup>. Similar principles can be adapted for the non-athlete by cycling between ketogenic and a moderate carbohydrate intake diet considering paleolithic principles. If followed systematically, this process could allow for the adaptation to ketosis without suffering the potential longer-term downfalls, as mentioned above.

Varying the type and timing of fasting also works for a variety of conditions. A study examining the effect of a fasting-mimicking diet on mice, as well as individuals with multiple sclerosis (MS), found significant improvements in MS symptoms and quality of life, as well as a complete reversal of symptoms in the mice<sup>76</sup>. Again, researchers believed that the fasting allowed for the drop in immune cells with the regeneration of healthy immune cells once refeeding began. Thus cycling through various types of fasting can also have benefits, rather than subscribing to only one pattern.

The variation of diet also addresses the adherence or feelings of deprivation an individual may feel. Adherence to a diet long term remains an issue for most people. A study attempting to compare low fat and low carb diets showed no difference between the two diets with regards to weight loss. However, although participants in the low carb group were told to eat less than 20 grams of carbohydrate, they ended up eating significantly more carbohydrates of more than 100 grams per day<sup>77</sup>. Would the success rate between the two diets have been better if participants in the low carb group knew they could increase their carbohydrate intake once or twice a week?

<sup>75</sup> McConell, G et al. "Effect of timing of carbohydrate ingestion on endurance exercise performance." *Medicine and science in sports and exercise* vol. 28,10 (1996): 1300-4. doi:10.1097/00005768-199610000-00014

<sup>76</sup> Choi, In Young et al. "A Diet Mimicking Fasting Promotes Regeneration and Reduces Autoimmunity and Multiple Sclerosis Symptoms." *Cell reports* vol. 15,10 (2016): 2136-2146. doi:10.1016/j.celrep.2016.05.009

<sup>77</sup> Gardner, Christopher D et al. "Effect of Low-Fat vs Low-Carbohydrate Diet on 12-Month Weight Loss in Overweight Adults and the Association With Genotype Pattern or Insulin Secretion: The DIETFITS Randomized Clinical Trial." *JAMA* vol. 319,7 (2018): 667-679. doi:10.1001/jama.2018.0245

Diet variation also addresses plateaus, so the body does not get overly stressed or adapted<sup>78</sup>. Alternating between days of higher intake of carbohydrates and protein will help the body feel safe so that it does adapt to starvation mode. In combination with fasting, varying intake can help stimulate the periods of growth and stem cell regeneration via the mTOR pathway in between periods of autophagy<sup>79</sup>. The variation between dietary intake can also help to decrease the stress response and release of cortisol, as mentioned above.

### **Diet variation: A new future for wellness**

Diet variation addresses all the critical evolution aspects discussed above. Cycling between diets that we know have positive benefits while utilizing periods of fasting (whether intermittent or more extended) provides solutions to the issues with modern eating patterns: an overabundance of foods, an alteration in the timing of eating, the quality of the food, and the balance of the macronutrients.

There will always be a new fad diet. However, instead of only looking forward to the next quick fix, the solutions to improved diet and health-related outcomes may require research to also look back in history. Ancestral health patterns are essential to take into consideration when adjusting for modern-day dietary patterns. The combination of timing with health-promoting dietary intake strategies supports an exciting new future of wellness.

<sup>78</sup> Greenway, F L. "Physiological adaptations to weight loss and factors favoring weight regain." *International journal of obesity (2005)* vol. 39,8 (2015): 1188-96.

doi:10.1038/ijo.2015.59

<sup>79</sup> Pompa, Daniel. *Beyond Fasting*. Revelation Health, 2019.