Ketogenic Program

Nutrition Masters Course

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Learning Objectives

• Review the impact of dietary macronutrient composition in human health, with a focus on low-carbohydrate approaches

• Understand the physiology and mechanisms of action of ketogenic approaches

• Discuss the clinical implications of ketogenic diets, from peripheral metabolism to brain health

• Examine nutritional ketosis: safety and monitoring

• Explore supporting factors for ketogenic lifestyle
  o Nutritional supplement support (e.g. medium-chain triglycerides [MCT], beta-hydroxybutyrate [βHB])
  o Collagen supplementation as adjunct wellness support
  o Fasting protocols
One diet doesn’t fit all:
Diets with different compositions of fat, protein, and carbohydrates

• Different diets varying in their fat, protein, and carbohydrate composition have been shown to successfully support weight loss and benefit cardiovascular disease and diabetes\(^1\)

• Diets that are tailored to the patient’s metabolic and health status, as well as personal and cultural preferences, may have the best chance for long-term success

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

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High carbohydrate intake and its impact on human health

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


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Benefits of low carbohydrate intake on human health

- In a study with type 2 diabetics, a low-carbohydrate ketogenic diet led to greater improvements in glycemic control, and more frequent medication reduction/elimination than the low glycemic index diet.

- In a study of highly trained ultra-endurance athletes, a long-term, low carbohydrate ketogenic diet resulted in high rates of fat oxidation.

- The low-carbohydrate ketogenic diet has also been shown to induce significant weight loss and improve fatty liver disease.

- Low-carbohydrate diet is associated with better vigilance attention and reduced self-reported confusion.

- In a preclinical study, a low carbohydrate diet slowed cancer development and progression.

2. Volek JS et al. *Metabolism* 2016; 65(3):100-10
Evolution of ketogenic diets (KD)

1. Wheless JW *Epilepsia* 2008; Suppl 8:3-5
12. Clarke K et al. *Regul Toxicology Pharmacology* 2012; 63(2)

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What are ketone bodies and how are they produced?

- Production of ketone bodies in the liver is a normal physiological process

- When glucose availability is low (for example during fasting, prolonged exercise, or when following a low carbohydrate diet plan), and the body utilizes fat to produce ketone bodies which are used as an alternative fuel source

- The main endogenous ketone bodies are acetone, acetoacetate and beta-hydroxybutyrate (βHB)\(^1\)\(^-\)\(^2\)

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What is ketosis?

- When ketone bodies accumulate in the bloodstream (>0.5 mmol/L), causing a metabolic state called ketosis

- The most efficient approach that results in nutritional ketosis is following a ketogenic diet¹

What is a ketogenic diet?

- Low carbohydrate (<50g/day)
- High fat (generally ~70% daily energy)*
- Adequate protein (~20% daily energy)*

- Some clinical indications require more strict adherence (e.g. epilepsy)

* Depending on overall kcal intake and physical activity

β-hydroxybutyrate (βHB): much more than an energy source

• In addition to acting as an energy molecule, βHB has a variety of cell signal functions, highlighting its broad regulatory role

• For instance, βHB can modulate epigenetic mechanisms and interact with cell surface receptors

• These mechanisms likely play a large role in mediating βHB’s effects on cellular protection and reduced oxidative stress

• These regulatory functions serve to link the outside environment to cellular function and gene expression, highlighting its implications for the pathogenesis and treatment of metabolic diseases

Which fuel tank do you want to access?

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

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

Ketogenic diet
• Low carbohydrate
• High fat
• Adequate protein

Reduced circulating glucose and insulin due to reduced dietary carbohydrate intake

- Increased ketone bodies (βHB, acetoacetate, acetone) in circulation and utilization by brain as fuel source
- Increase in liver fatty acid oxidation
- Increased production of ketone bodies using FFA (from dietary source and released from adipose tissue) for ketone body production within liver mitochondria
- Increased use of FFA as energy source in skeletal muscle with preservation of glycogen stores

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Ketogenic diet’s impact on:

Weight management
Cardiometabolic risk markers
Insulin resistance
Type 2 diabetes
Carbohydrate intake and obesity prevalence over time in the US between 1960 and 1997

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

Link between high carbohydrate intake and onset of obesity

High carbohydrate intake → Blood glucose → Insulin levels → De novo lipogenesis → Fat accumulation → Obesity
Can ketogenic diets be used for weight management?

- In subjects with BMI >30kg/m², intervention with:
  - LCKD: Energy-reduced, low-carbohydrate ketogenic diet or
  - LFD: Low-fat diet

- Over 24 weeks, the change in body weight was −12.0 kg (95% CI, −13.8 to −10.2 kg) in the LCKD group compared with −6.5 kg (95% CI, −8.4 to −4.6) in the LFD group

- 61% of recipients on LCKD lost >10% of their initial body weight at 24-weeks

Adapted from: Yancy et al. *Annals of Internal Medicine* 2004;140(10):769-777
Change in appetite in response to ketogenic low carbohydrate diet

Method

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

Conclusions

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

*defined as those resulting in raised fasting β-hydroxybutyrate to ≥0.3mM, positive urinary ketone dipstick or dietary prescription consistent with inducting ketosis

Adapted from: A. A. Gibson et al. Obesity review 2015; 16(1): 64–76
The effectiveness of ketogenic diet to combat the adverse metabolic pathologies of obesity

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

Gibas MK, Gibas KJ. Diabetes & Metabolic Syndrome 2017;11(1):385-390
How ketogenic diets regulate obesity and its associated pathologies?

**Weight loss**
- Reduction in appetite and hunger
- Reduction in lipogenesis
- Increased lipolysis
- Increased thermic effect of proteins

**Diabetes**
- Reduction of HbA1C, blood glucose and insulin levels
- Reversal of hepatic insulin resistance

**Cardiovascular risk parameters**
- Reduction of endogenous cholesterol synthesis
- Reduction of blood cholesterol and TGs
- Increased LDL particle size
- Reduction of blood insulin levels

Ketogenic diet’s impact on:

Athletic Performance
Keto-adaptation enhances endurance performance and body composition in athletes

- Keto-adaptation **improves endurance capacity** and **improves fat mobilization and oxidation** during exercise performance\(^1,2\)

- Liver and muscle **glycogen deposits are maintained**, attenuating glycogen depletion observed in athletes consuming high-carbohydrate diets\(^1\)

- Keto-adaptation **improved aerobic and anaerobic exercise capacity**, as well as body composition in endurance athletes

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Ketogenic diet’s impact on:

Fuel for the brain
Alzheimer’s Disease
Cognition and aging
The human brain is extraordinarily expensive

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


- During the execution of cognitively demanding tasks, a decrease in hippocampal glucose levels is observed\(^2\)
- More complex tasks deplete hippocampal glucose levels further

* **Cognitive performance is limited by fuel availability in the hippocampus**

Impaired brain glucose utilization and cognitive decline

The healthy young brain relies solely on glucose to obtain energy for its functional and structural needs\(^1\)

During healthy aging, brain glucose uptake is 10-15% lower and can be up to 35% lower in certain brain areas in neurological disorders such as Alzheimer’s Disease (AD)\(^1-5\)

**Brain uptake of ketones appears to remain normal in the brains of patients with Alzheimer’s Disease\(^5\)**

Can the brain use ketone bodies?

• Common misconception: brain can only use glucose

• Ketone bodies are the only alternative source of energy for the brain (as it cannot utilize FFAs)

• Both rodent and human studies have shown increased uptake of ketone bodies by the brain\(^1,2\) following:
  ✓ Peripheral infusion of ketones
  ✓ Prolonged fasting
  ✓ Ketogenic diet

Can the brain use ketone bodies?

• When obese subjects underwent prolonged fasting (water access only for 4 to 6 weeks), researchers were able to investigate cerebral energy metabolism during nutrient (glucose) deprivation.  

• They observed that **up to 70% of brain’s energy demands were provided by ketone bodies** available in circulation (blood) and taken up by the brain.

Can the brain use ketone bodies?

- Higher circulating levels of ketone bodies result in higher brain uptake and utilization of ketones for its energy demands$^1$

- Preserved uptake and utilization of ketone bodies in the brains of mild cognitively impaired (MCI) patients, whereas glucose uptake and utilization decreases 20-30%$^{1-5}$

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

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Brain health comprises more than memory

- Emerging science suggests that optimizing cerebral energy metabolism with ketone bodies may benefit a wide array of neurological conditions\(^1\)

- Research groups have recently started investigating the potential therapeutic benefits of ketogenic diets on neurodevelopmental and affective disorders\(^1,2\)

- **Subjective reports and anecdotal evidence** suggest a beneficial effect of ketogenic diets on mood\(^3\), anxiety and attention and further research is needed to validate these claims

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Testing and Monitoring
How to test ketone levels and monitor ketosis?

- **Urine:** measures urinary excretion of acetoacetate—although this is the easiest and most common test, it may provide false negative results following keto-adaptation

- **Blood:** finger stick measuring circulating βHB levels—most accurate

- **Breath:** measures breath acetone

**Optimal levels of ketosis**
- Overnight fasting: 0.2-0.5mM
- Nutritional Ketosis (KD): 0.5-3.0mM
- KD with exogenous ketones: 0.5-8.0mM
- Ketoacidosis: >10mM

Supporting factors for ketogenic lifestyle
Supporting factors for ketogenic lifestyle

- With growing popularity of low-carbohydrate and ketogenic diets, interest has increased in exploring additional nutritional strategies and solutions to facilitate:
  - Achieving or sustaining ketosis
  - Keto-adaptation process
  - Convenience to ensure long-term adherence to ketogenic program

- Examples considered:
  - Exogenous Ketones (βHB)
  - Medium Chain Triglycerides (MCT)
Exogenous ketone (βHB) salt

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

1. Kesl et al. *Nutrition & Metabolism* 2016;13:9,
2. Caminhotto RO et al. *Nutrition & Metabolism* 2017; 14:31
Very limited human intake data for βHB salt

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

- **Primary objective**
  - To characterize the change in circulating ketone bodies over a 4-hour period after consumption of varying doses of βHB, compared with placebo control.

- **Secondary objective**
  - To assess tolerance and adverse events in response to acute intake of each formulation.

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* Data on file. *Manuscript in development*
Study Design*

**STUDY TIME-LINE**

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 3*</th>
<th>Week 3 – 5**</th>
<th>Week 5-7</th>
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<tbody>
<tr>
<td>Screening</td>
<td>Enrollment</td>
<td>Cross-over design</td>
<td>Optional 2 weeks follow-up</td>
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<table>
<thead>
<tr>
<th>Study Activity</th>
<th>Study Time</th>
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<tbody>
<tr>
<td>Screening</td>
<td>Week 1</td>
</tr>
<tr>
<td>Enrollment</td>
<td>Week 3*</td>
</tr>
<tr>
<td>Cross-over</td>
<td>Week 3 – 5**</td>
</tr>
<tr>
<td>Placebo control</td>
<td>Week 5-7</td>
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</table>

Each treatment arm completed in random order. Each treatment delivered on a separate study day, each separated by a wash-out period of 2-7 days.

- Enrollment must take place within 2 weeks of screening date
- Each study visit can be separated by up to a 1 week wash out period (minimum 2 days)

- 10 generally healthy men and women completed all 3 study arms
- All subjects were white
- 2 men and 8 women were enrolled and included in the final analysis

# On basis of reported medical history and results of screening bloods (liver and renal function tests, comprehensive metabolic panel)

<table>
<thead>
<tr>
<th>PR#</th>
<th>Treatment</th>
<th>βHB dose</th>
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<tbody>
<tr>
<td>PR-761</td>
<td>βHB salt – Dose 1</td>
<td>11.7g βHB</td>
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<tr>
<td>PR-763</td>
<td>βHB salt – Dose 2</td>
<td>5.85g βHB</td>
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<tr>
<td>PR-762</td>
<td>Placebo control</td>
<td>No βHB</td>
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Subject characteristics

<table>
<thead>
<tr>
<th>Description</th>
<th>Mean</th>
<th>SD</th>
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<tr>
<td>Age (years)</td>
<td>31.4</td>
<td>11.96</td>
</tr>
<tr>
<td>Fasting βHB (mmol/L)</td>
<td>0.17</td>
<td>0.08</td>
</tr>
<tr>
<td>Body mass index (BMI) (kg/m²)</td>
<td>23.7</td>
<td>1.28</td>
</tr>
</tbody>
</table>

* Data on file. Manuscript in development
Acute intake of βHB salt increases circulating βHB concentrations within 15 minutes*

**Data displayed as mean ± SEM. Differences between groups assessed with Friedman test, with Dunnett’s test. Between-treatment differences denoted as a, b with treatments not sharing a letter considered significantly different (p<0.05).**

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

Additional considerations

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

*Data on file. Manuscript in development*
Choosing the right fat for ketogenic programs

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

• MCTs contain 6 to 12 carbon atoms, including caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), and lauric acid (C12:0)

• In the liver, MCFA can freely cross the inner mitochondrial membrane, while other types of fatty acids must enter in a more regulated manner

• This more rapid absorption of MCFA into the inner mitochondrial space transiently increases ketone body formation¹

MCFA= medium chain fatty acids, OM = outer membrane, IM = inner membrane
Effects of MCTs on weight loss, body composition, satiety and cognition:

• A meta-analysis of randomized controlled trials has shown that replacement of long-chain triglycerides (LCT) with MCT (combination of C8:0 and C10:0) in the diet resulted in greater reduction in body weight and more favorable changes in body composition in both healthy and overweight individuals\(^1\)

• MCTs supplementation (C8:0 and C10:0) increased energy expenditure and lipid oxidation compared with LCTs\(^2\)-\(^3\)

• In healthy and overweight men, supplementation with MCT increased satiation at the next meal and reduced food intake compared to LCT \(^3\)-\(^4\)

• Ketones derived from MCTs improved cognition in diabetic and AD patients and attenuate neurodegeneration in mouse models of ALS, MS and AD\(^5\)-\(^7\)

\(^1\) Mumme K. & Stonehouse W. *Journal of the Academy of Nutrition and Dietetics* 2015; 115:249-263
\(^2\) St-Onge M et al. *Obesity Research* 2003; 11(3):395-402
\(^5\) Zhao W et al. *PLoS ONE* 2012; 7(11):e49191
\(^7\) Henderson S et al. *Nutrition & Metabolism* 2009; 6:3
Majority of human clinical studies have been performed with the mixture of C8+C10

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>C8 EURavia®</th>
<th>C10 EURavia®</th>
<th>C8+C10 EURavia®</th>
</tr>
</thead>
<tbody>
<tr>
<td>increased satiety</td>
<td></td>
<td></td>
<td>St-Onge M et al. <em>Obesity Research</em> 2003; 11(3):395-402</td>
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</tbody>
</table>

Additional actions including activation of PPARy and improvements in mitochondrial efficiency have been demonstrated with both C8 and C10

Emerging science—separating fact from fiction

<table>
<thead>
<tr>
<th>Headlines</th>
<th>Study findings</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>KD increases longevity</td>
<td>Preclinical studies on male mice show that KD <em>reduced</em> midlife mortality</td>
<td>Newman JC et al. <em>Cell Metabolism</em> 2017; 26:547-57</td>
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<tr>
<td></td>
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<td>Roberts MN et al. <em>Cell Metabolism</em> 2017; 26:539-46</td>
</tr>
<tr>
<td>KD induces mental clarity</td>
<td>Preclinical studies on male rodents show that KD <em>improves</em> learning and memory outcomes in models of neurodegenerative diseases</td>
<td>Kashiwaya Y et al. <em>Neurobiology of Aging</em> 2012; 1-10</td>
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<td>Reger M et al. <em>Neurobiology of Aging</em> 2004; 25:311-14</td>
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<td></td>
<td>Zhao W et al. <em>PloS ONE</em> 2012; 7(11):49191</td>
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<tr>
<td>KD improves cognition</td>
<td>KD research has historically focused on neurological disorders whereas cognitive outcomes in healthy subjects have been <em>anecdotally</em> reported</td>
<td>Kashiwaya Y et al. <em>Neurobiology of Aging</em> 2012; 1-10</td>
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<td>Zhao W et al. <em>PloS ONE</em> 2012; 7(11):49191</td>
</tr>
<tr>
<td>KD and mood</td>
<td>Preclinical studies have shown <em>anxiolytic effects</em> associated with KD whereas few case reports have been published showing benefits in humans</td>
<td>Ari C et al. <em>Frontiers in Molecular Neuroscience</em> 2016; 9:137</td>
</tr>
<tr>
<td></td>
<td></td>
<td>El-Mallakh RS &amp; Paskitti ME <em>Medical Hypothesis</em> 2001; 57(6):724-26</td>
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<tr>
<td></td>
<td></td>
<td>Bostock ECS et al. <em>Frontiers in Psychology</em> 2017; 8:43</td>
</tr>
<tr>
<td>Collagen is necessary for ketogenic lifestyle and helps build muscle</td>
<td>Collagen contains only low levels of the essential amino acids necessary for muscle protein synthesis. It can, however, be used as <em>adjunct wellness support</em> due to a number of benefits associated with collagen supplementation</td>
<td>Fu Y et al. <em>Critical Reviews Food Science Nutrition</em> 2018; 2:1-17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rodriguez MIA et al. <em>Journal of Cosmetic Dermatology</em> 2018; 17:20-26</td>
</tr>
</tbody>
</table>
Collagen supplementation as adjunct wellness support to ketogenic lifestyle

- Preclinical and clinical studies show that supplementation with collagen:
  - Supports **healthy joints in athletes** (both healthy and with knee problems)\(^1,2\)
    - Improvements in activity-related pain intensity
    - Reduction of risk of joint deterioration
  - Supports **bone health**\(^3,4\)
    - Stimulates the proliferation and differentiation of osteoblasts
    - Increased bone mineral density in postmenopausal women
  - Supports **extracellular matrix and cartilage**\(^5,6\)
    - Stimulation of chondrocytes to synthesize extracellular cartilage matrix
    - Increased collagen synthesis and decreased extracellular matrix disruption
  - Improves **age-related effects on skin**\(^7,8\)
    - Increased skin hydration and elasticity
    - Reduced appearance of eye wrinkle

<table>
<thead>
<tr>
<th>Fasting Protocol</th>
<th>How to implement</th>
<th>Benefits</th>
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<tbody>
<tr>
<td><strong>Time Restricted / Intermittent Fasting (IF)</strong></td>
<td>6-8h daily eating window (&gt; 16h fast)</td>
<td>• Improved glycemic regulation and reduced CRP&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>• Aligned with circadian rhythms&lt;sup&gt;2&lt;/sup&gt;</td>
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<td><strong>Alternate Day Fasting</strong> (also considered a form of IF)</td>
<td>No caloric intake (food or drinks) on fasting days, which alternate with ad libitum eating days</td>
<td>• Improved markers of oxidative damage and inflammation in asthma patients&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
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<td></td>
<td></td>
<td>• Body fat, blood pressure, and glucose metabolism improved in obese subjects&lt;sup&gt;4, 5&lt;/sup&gt;</td>
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<tr>
<td><strong>5:2 Fasting</strong> (also considered a form of IF)</td>
<td>Ad libitum eating 5 days and restricted calories (500-600 kcal) for 2 days (can be consecutive, but not necessarily)</td>
<td>• Reduced oxidative stress and inflammation in overweight women at risk for breast cancer&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
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<td></td>
<td></td>
<td>• Reductions in body weight and fat and improved mood in elderly men&lt;sup&gt;7&lt;/sup&gt;</td>
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<tr>
<td><strong>Prolonged Fasting</strong></td>
<td>No caloric food or drinks for ≥ 72h</td>
<td>• Reduction in circulating glucose, insulin, and IGF-1 levels&lt;sup&gt;8&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td>• Reduced side effects when chemotherapy combined with fasting&lt;sup&gt;9&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td>• Decreased blood pressure in hypertensive subjects&lt;sup&gt;10&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>• Decreased pain and inflammation in RA patients&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Short-term Fasting</strong></td>
<td>No caloric food or drinks for &lt; 72h</td>
<td>• 5-fold increase in GH&lt;sup&gt;12&lt;/sup&gt; and improved BDNF&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Fasting Mimicking Diet (FMD)</strong></td>
<td>Diet consisting of plant-based, low protein, reduced caloric intake for 3 cycles of 5 days/month</td>
<td>• Improved metabolic parameters associated with age-related conditions&lt;sup&gt;14, 15&lt;/sup&gt;</td>
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<td>• Improved overall quality of life scores in multiple sclerosis patients and reduced inflammatory profile in preclinical model&lt;sup&gt;16&lt;/sup&gt;</td>
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<td></td>
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<td>• Increased tumor sensitization to chemotherapy&lt;sup&gt;17&lt;/sup&gt;</td>
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Fasting and Keto

- **Positive metabolic and cellular effects** that affect oxidative damage and inflammation, optimize energy metabolism, and enhance cellular protection\(^1\)
- **Increased metabolic flexibility** and facilitates switch to fat-burning\(^2\)
- **Hormesis concept**: adaptive response to moderate stress resulting in increased cytoprotective and restorative mechanisms\(^3\)

**Benefits to a ketogenic lifestyle**

- **Increased lipolysis**\(^2\) possibly reduces time needed for keto-adaptation process
- **Reduced glucose and higher ketone levels**: 12-24h fasting depletes hepatic glycogen, leading to metabolic switch into fat-burning mode and utilization of ketones and fatty acids\(^2\)
- By facilitating ketogenesis and reducing keto-adaptation time, it may shorten period of time with ‘keto-flu’ symptoms

**Caution**

- Fasting regimens have not been investigated in children, elderly, nor underweight individuals
- Fasting periods longer than 24h should be overseen by healthcare provider
- Proper intake of non-caloric fluids to ensure hydration
- Possible effects on circadian rhythms of endocrine and gastrointestinal systems

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## Emerging science—novel research areas

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<th>Cognition</th>
<th>Stress</th>
<th>Microbiome</th>
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<td>• Longevity</td>
<td>• Augmentation</td>
<td>• Resilience</td>
<td>• Gut-brain axis</td>
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<tr>
<td>• Reduce age-associated morbidity</td>
<td>• Prevention of decline</td>
<td>• Prevention</td>
<td>• Increased diversity</td>
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<td></td>
<td>• Biohacking</td>
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In Summary

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

- **Ketone bodies:**
  - Efficient fuel source
  - Improve mitochondrial bioenergetics
  - Cellular signaling molecule
  - Preserved uptake by the brain
