

Intermittent Fasting:

What it is, and the effect on weight loss and other metabolic parameters



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Disclosures

- I have no financial disclosure or conflict of interest with the presented material in this presentation

Disclaimer

- Before starting any weight loss plan, individuals should consult with a healthcare professional, and/or someone from diabetes care team, and/or a dietitian to see which plan would be safe and effective to lose weight and that is sustainable for them.
- Patients with diabetes who are interested in intermittent fasting should be encouraged to engage in fasting with guidance from a healthcare practitioner, including physicians, nurse practitioners, physicians' assistants, certified diabetes educators, or registered dietitians.

Agenda

1. Provide background information on why we need to address importance of nutrition and diets
2. Bridge knowledge gap related to fasting and how intermittent fasting works
3. Introduce the types of intermittent fasting
4. Demonstrate impact of intermittent fasting on weight loss, metabolic parameters, Diabetes and cardiovascular markers
5. List the benefits and risks of intermittent fasting
6. Provide tips to best monitor patients who want to start intermittent fasting

Want to Live Longer and Better?

1. Eating a healthy diet
2. Exercise regularly
3. Maintain a healthy body weight
4. Drink only in moderation
5. Not smoking
6. Get good sleep
7. Have healthy and supportive relationships



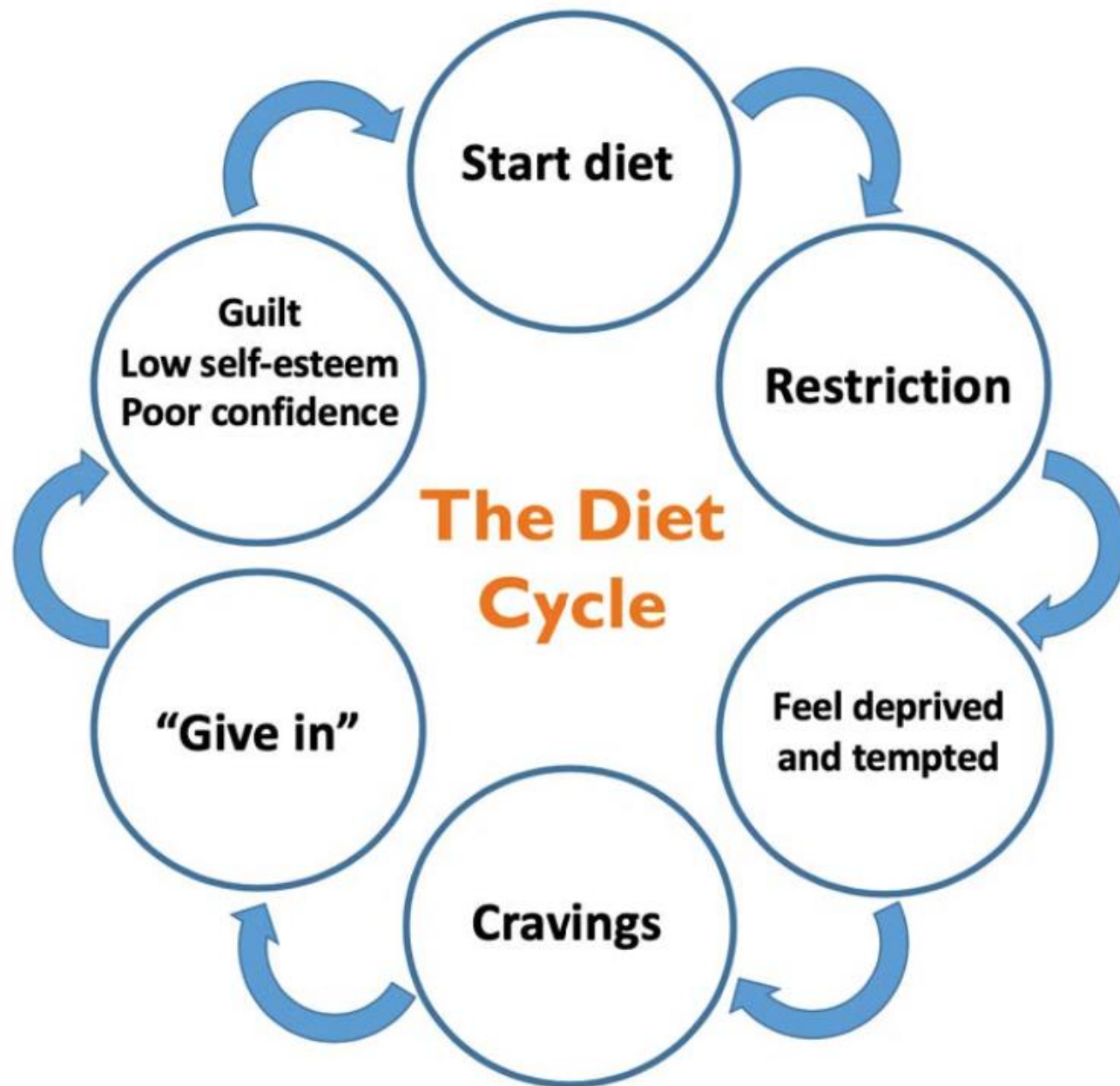
DIET AND NUTRITION

Impact of Weight Gain on Health

- As of 2018, >72%* of Americans are overweight or obese — almost 3X more than in 1980.
- Rising rates of diabetes, atherosclerosis, heart attacks, strokes, inflammatory conditions, cancer, etc.
- Metabolic syndrome affects 30% of the U.S. population, and confers a 5-fold increase in the risk of T2DM and doubles the risk for CVD over 5–10 years**
- Americans have become a nation of snackers
 - People eat for more than 12 hours a day
- Adherence to “weight loss diets” is very low in the long run
- Most “weight loss diets” are not successful at keeping the weight off

* <https://www.niddk.nih.gov/>

**Alberti et al., 2009; Circulation, 2009



Which diet plan leads to most weight loss?

1. Plant-based diet
2. Mediterranean diet
3. DASH diet
4. Vegan diet
5. Raw food diet
6. Paleo diet
7. Gluten-free diet
8. Keto diet
9. Intermittent Fasting/Other fasting
10. There is NO ONE ANSWER

Best Diets 2022



#1 Mediterranean Diet

#2 DASH Diet(tie)

#2 The Flexitarian Diet(tie)

#4 MIND Diet

#5 Mayo Clinic Diet(tie)

#5 TLC Diet(tie)

#5 Volumetrics Diet(tie)

#5WW (Weight Watchers) Diet(tie)

#9 Vegetarian Diet

#10 Nordic Diet

#27 Intermittent Fasting^

*Ranked for Best Diets Overall by panel of 27 nationally recognized experts in diet, nutrition, obesity, food psychology, diabetes and heart disease in:

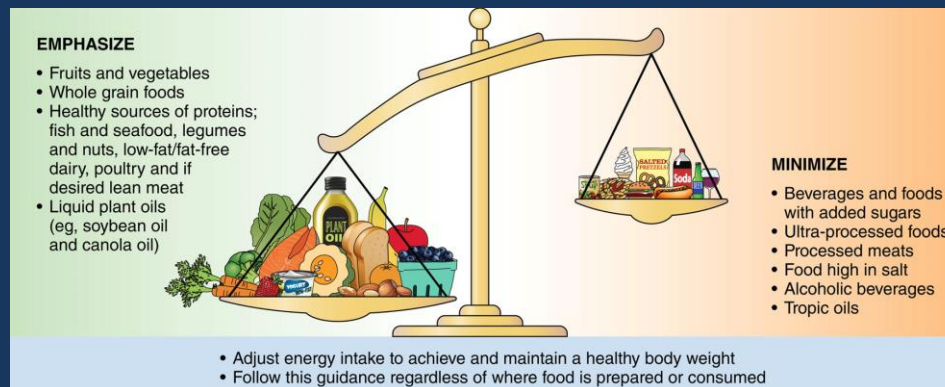
- Its safety
- How easy it is to follow
- Its ability to produce short-term and long-term weight loss
- Its nutritional completeness
- Its potential for preventing and managing diabetes & heart disease

^A behavioral intervention tool and not a “diet”

Source: U.S. News.
Available at
<https://health.usnews.com/best-diet>

National Guidelines On Nutrition

- **Dietary Guidelines for Americans:** Heart-healthy dietary patterns (i.e., Mediterranean style, DASH style, healthy vegetarian diets, etc.)
- There is insufficient evidence to support any existing popular or fad diets (ie., ketogenic diet; intermittent fasting) to promote heart health
- **The American Diabetes Association** recommends weight loss for overweight and obese patients; which can help lower your A1c and lower risk for heart disease.
 - They do not recommend fasting as a technique for diabetes management



Circulation

Food/Nutrition

- Nutrition plays a significant role in:
 1. Health promotion
 2. Disease prevention
 3. Disease management



1. **WHAT** to eat and not eat
2. **HOW MUCH** to eat
3. **WHEN** to eat or not eat

If food is medicine, why isn't it taught at medical schools?

- Poor diet continues to be one of the biggest contributors to chronic disease and mortality in the U.S.
- On average, students in US medical schools spend <1% of lecture time learning about diet (source: Harvard Food Law and Policy Clinic)
- Federal government and accreditation groups do not strictly enforce any minimum level of diet instruction
- When the curriculum was developed, we weren't looking at the high rates of obesity and chronic diseases
- Need: Build a new foundation because what we have is not working

Nutritional Framework

1. Dietary Restriction: Limiting **WHAT** you do or do not eat
 - Sugar, carbohydrates, dairy, meat
 - Ketogenic, Vegan
2. Caloric Restriction: Limiting **HOW MUCH** you eat (most common way we think about diets)
3. Time Restriction: **WHEN** you eat or do not eat

When To Eat?



Fasting and Intermittent Fasting:

Fasting: Period of voluntary abstinence from food and drink.

****More than 24hrs after last bite of food****

Intermittent Fasting: Eating pattern that alternates between periods of eating and fasting

*Caloric drinks or drinks that can mimic glucose

Fasting

Short-Term Intermittent

**Time-Restricted
Eating (TRE)**

**Modified
Fasting**

**Alternate-Day
Fasting**

Long-Term

**Fasting
Mimicking
Diet
(5-Days)**

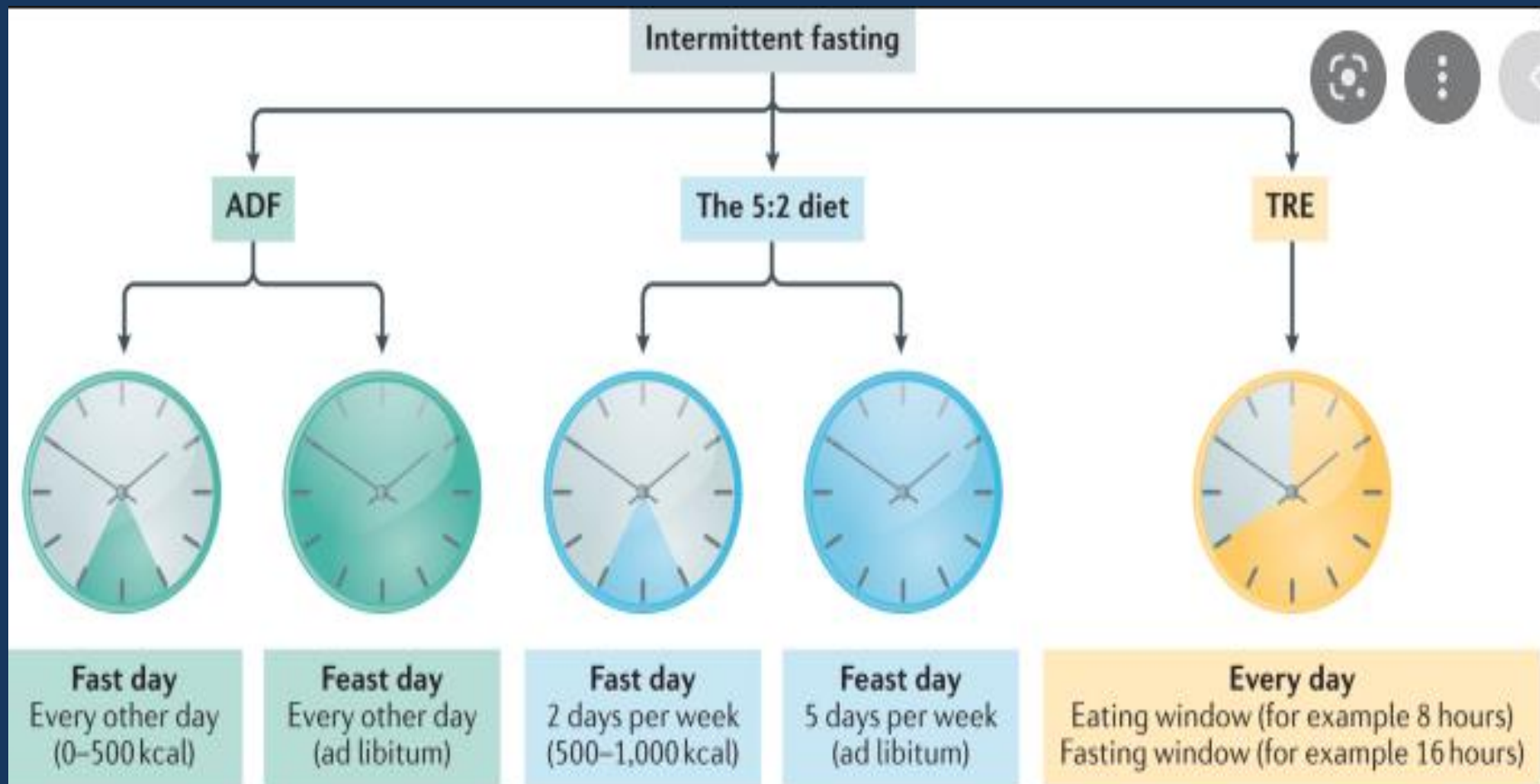
**Fasting
Mimicking
Diet
(8-Days)**

**Prolonged
Fasting**

72-Hour Cutoff

Shallow Fasted State

Deep Fasted State



ADF= Alternate day fasting

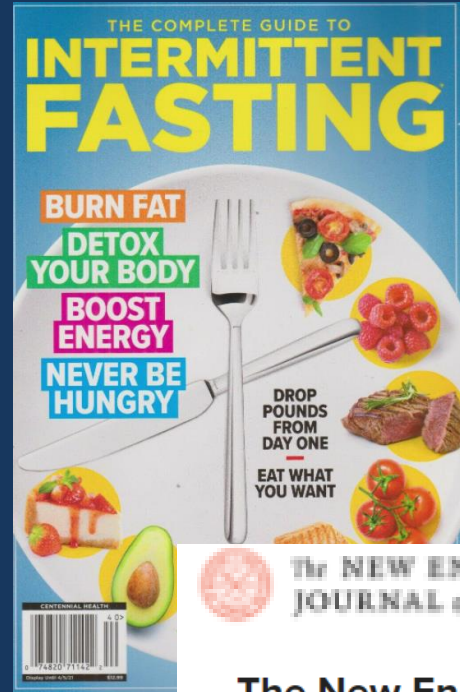
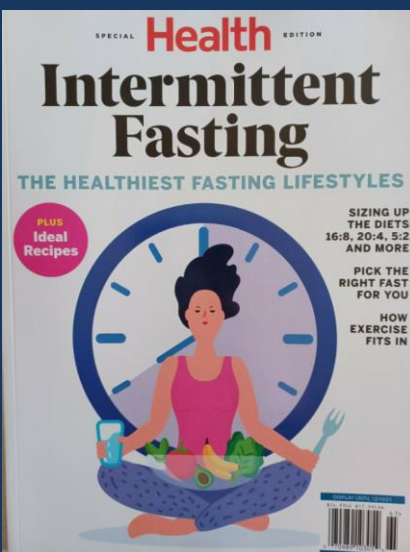
TRE=Time-restricted eating

TRE: The most common type of intermittent fasting

Source: Varady, K.A., Cienfuegos, S., Ezpeleta, M. *et al.* Clinical application of intermittent fasting for weight loss: progress and future directions. *Nat Rev Endocrinol* **18**, 309–321 (2022).

Intermittent Fasting

- Intermittent Fasting is an eating pattern, not a “diet”
 - Does not specify what foods a person should eat or avoid
- Has mild/modest weight loss impact
 - ~4%-8% weight loss during trials of 8-12 weeks; similar to that attained with a calorie-restricted diet.
- May have benefits to health, aging, and illness
 - Reduce the risk of diabetes
 - Reduce cell damage from inflammation and oxidation
 - Lower blood pressure
 - Improve memory
 - Improve endurance
- We do not fully understand the specific mechanisms, the beneficial effects involve **metabolic switching** and cellular stress resistance
- Is NOT for everyone
 - Not for children, type 1 diabetics, and diabetics using insulin, women who are pregnant or thinking about trying to conceive or is breastfeeding, if underweight, or if you have a history of eating disorders



The New England Journal of Medicine Review of the Effects of Intermittent Fasting on Health, Aging and Disease

JAMA
Network | **Open**™

Original Investigation | Nutrition, Obesity, and Exercise

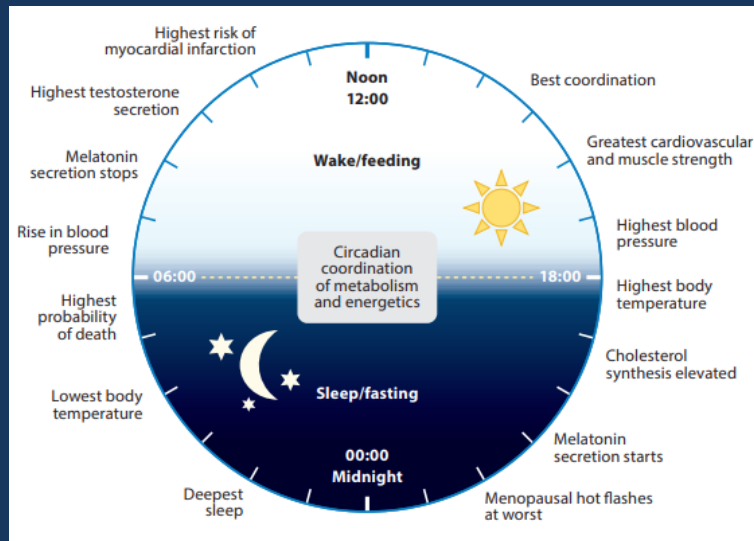
Intermittent Fasting and Obesity-Related Health Outcomes An Umbrella Review of Meta-analyses of Randomized Clinical Trials

JAMA Internal Medicine | **Original Investigation**

Effects of Time-Restricted Eating on Weight Loss and Other
Metabolic Parameters in Women and Men With Overweight and Obesity
The TREAT Randomized Clinical Trial

Wake/feeding

Liver	Glycogen, cholesterol, and bile acid synthesis
Pancreas	Insulin secretion
Fat	Lipogenesis, adiponectin production
Muscle	Glycolytic metabolism



Source: Annu. Rev. Nutr.
2017. 37:371–93

Sleep/fasting

Liver	Gluconeogenesis, glycogenolysis, mitochondrial biogenesis
Pancreas	Glucagon secretion
Fat	Lipid catabolism, leptin secretion
Muscle	Oxidative metabolism

What happens in your body each hour of fasting (times based from last calorie intake):

- 4-8 hours
 - Blood sugars fall; All food has left the stomach; Insulin is no longer produced
- 12 hours
 - Food consumed has been burned; Digestive system goes to sleep; Body begins healing process; Human Growth Hormone begins to increase; glycogen into glucose
- 14 hours
 - Body has converted to using stored fat as energy; Human Growth Hormone starts to increase dramatically
- 16 hours
 - Body starts to ramp up the fat burning
- 18 hours
 - Human Growth Hormone starts to skyrocket
- 24 hours- Autophagy begins (cellular clean up); Drains all glycogen stores; Ketones are released into the blood stream
- 36 hours-Autophagy 300% increase
- 48 hours-Autophagy increases 30% more; Immune system reset and regeneration; Increased reduction in inflammation response
- 72 hours- Autophagy maxes out

RESEARCH AND EVIDENCE

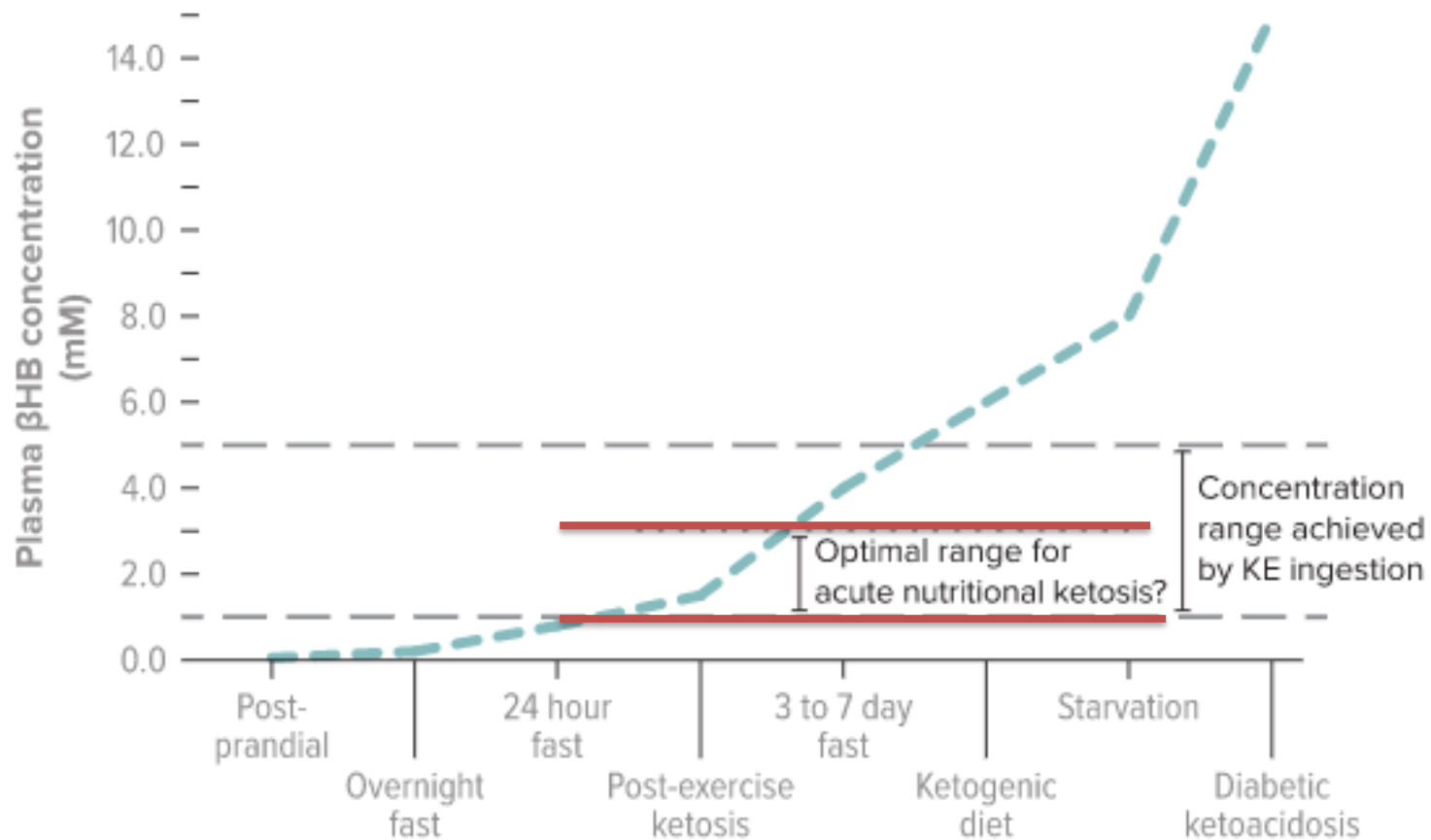
When we eat is as important as what/how much we eat

- Many studies conducted in laboratory/animal models (rats, monkeys, etc)
 - Showed weight loss, improvement in blood pressure, cholesterol, and blood sugars improve
 - Suppression of inflammation in the brain and improvements in cancers
- Human clinical trials:
 - Most have been short (a few weeks or months), limited study population, observational, conducted in overweight subjects, and focused on weight loss rather than metabolic/aging processes
- Human studies have shown that TRE is safe.
- TRE is no more effective than any other diets
 - Mild/Moderate weight loss (4%-8%)
 - No clear evidence on lifespan effects
 - Minimal information on safety in those with special medical conditions
- Humans are quite different from each other in terms of gender, size, age, genetics, environment, lifestyle, and other factors. An eating pattern that's found to help one person might not have the same effect on another.
- Weight loss is not the main driver of the health benefits observed

Research Evidence on TRE

- **Metabolic switching** is the key mechanism
 - Fasting triggers the body to switch its source of energy from glucose stored in the liver to ketones, which are stored in fat
- Ketogenesis starts and carries over into the non-fasting period and can improve glucose regulation, increase stress resistance and suppress inflammation
- Ketone bodies
 - Fuel used during periods of fasting
 - Potent signaling molecules that regulate the expression and activity of many proteins and molecules that are known to influence health and aging
 - They enhance the body's defenses against oxidative and metabolic stress and initiate the removal or repair of damaged molecules
- Magnitude of effect can be influenced by diet, sex, age, and genetic factors

Ketones rise with longer fasting times



SOURCE: M. EVANS ET AL / THE JOURNAL OF PHYSIOLOGY 2017

After a meal (post-prandial), ketone body levels in the blood are at their lowest. But they rise during fasts or after exercise. Ketone ester (KE) drinks or following a ketogenic diet also boosts levels. At the high levels seen in starvation and ketoacidosis, ketones can become a danger. Researchers speculate that an optimal range to improve athletic performance can be reached with a KE drink.

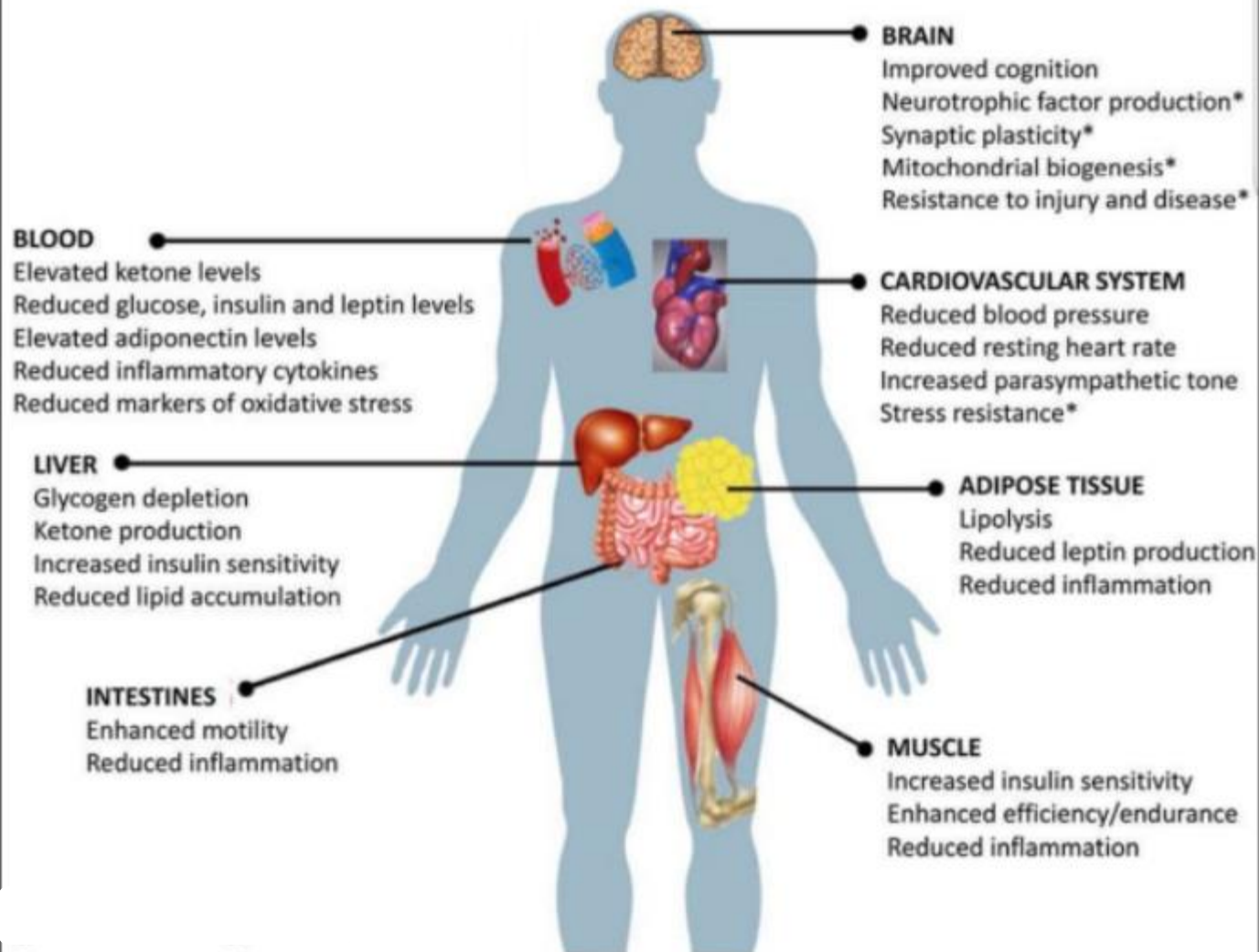
Research Evidence on TRE

- During fasting, cells are forced to cope with the lack of continuous glucose source, and engage in a coordinated adaptive stress response that leads to:
 1. DNA repair
 2. Increase in the expression of antioxidant defenses
 3. Autophagy
 4. Mitochondrial biogenesis
 5. Downregulation of inflammation

Metabolic Benefits of Intermittent Fasting (IF)

- Decreased fasting glucose
- Decreased fasting insulin
- Reduced insulin resistance
- Decreased levels of leptin
- Increased levels of adiponectin
- Initiates cellular repair processes
- Reduction in body weight

Intermittent Fasting (IF) Benefits

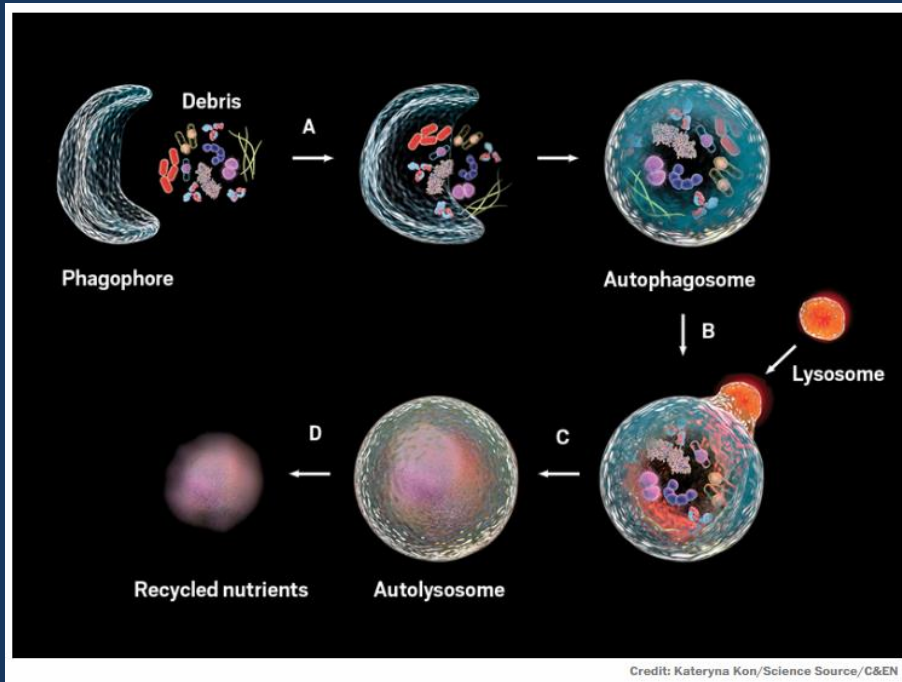


Source: Anton, S. D., et al. (2017). Flipping the Metabolic Switch: Understanding and Applying the Health Benefits of Fasting. *Obesity*, 26(2), 254–268.

Autophagy

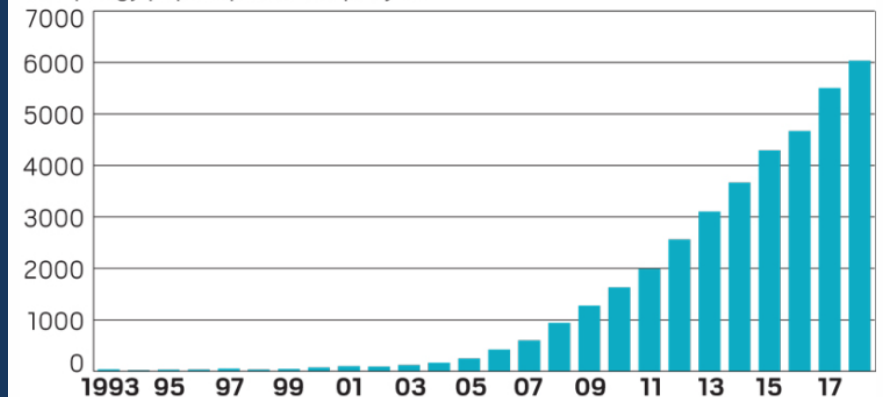
- Definition=“Self eating”
- Is a detox process where your body cleans out damaged cells/cellular components and regenerates new ones
- Helps the immune system by cleaning up toxins and infectious agents
- Occurs during sleep—because that's when we're fasting
- Can also be triggered by: Exercise, Curcumin (found in turmeric) root; in response to the stress brought on by fasting, calorie restriction or by certain medications.

Autophagy



The number of autophagy publications has soared in the past decade and shows no signs of slowing down.

Autophagy papers published per year



Sources: PubMed, accessed May 23, 2019.

In 2016, Nobel Prize was awarded for the discovery of autophagy genes. Several biotech companies launched with plans to develop drugs that either boost or inhibit autophagy to treat a diseases, including Alzheimer's and cancer.

Is Intermittent Fasting Safe for Type 2 Diabetes?

- The ADA doesn't recommend fasting as a technique for diabetes management. Lifestyle changes, including medical nutrition therapy and more physical activity, as the cornerstones for weight loss and good diabetes control.
- IF/TRE leads to some weight loss
- Other potential benefits include:
 - Improved insulin sensitivity
 - Lower blood pressure
 - Lower oxidative stress
 - Reduced appetite
 - Increased fat oxidation
- Risk of hypoglycemia and hyperglycemia, due to fluctuations in blood sugar during and after periods of not eating
- More research is needed to determine the long-term risks and benefits of intermittent fasting for people with diabetes



Cell Metabolism

Sources:

1. Vasim I, Majeed CN, DeBoer MD. Intermittent Fasting and Metabolic Health. *Nutrients*. 2022;14(3):631.
2. Grajower MM, Horne BD. Clinical Management of Intermittent Fasting in Patients with Diabetes Mellitus. *Nutrients*. 2019;11(4):873. Published 2019 Apr 18.
3. Wilkinson MJ, Manoogian ENC, et al. Ten-Hour Time-Restricted Eating Reduces Weight, Blood Pressure, and Atherogenic Lipids in Patients with Metabolic Syndrome. *Cell Metab*. 2020 Jan 7;31(1):92-104.

Table 2

Considerations and recommendations for adjustment of antidiabetic medications during intermittent fasting.

Class of Medication	Drugs	Risk of Hypoglycemia	Dose Adjustment	Comments
Biguanides	metformin	low	None	
Thiazolidinediones	pioglitazone, rosiglitazone	low	None	
Sulfonylureas	glyburide, glipizide, glimepiride	high	Skip that day for a 24-h fast; as utilized in one study [6], take half the dose for a partial day fast (i.e., when a meal is consumed at some point part way through the fasting day)	A caution for the half dose is that substantial education and monitoring may be required to avoid hypoglycemia [6]. Another study skipped the whole dose on any even partial fasting day, which is more conservative and cautious [8].
Meglitinides	nateglinide, repaglinide	moderate	Skip prior to a meal containing no carbohydrates	
DPP4 Inhibitors	saxagliptin, sitagliptin, alogliptin, linagliptin	low	None (or can skip on the day of fasting)	The dose can be skipped because there is no benefit to taking it and this would reduce healthcare costs to the patient.
SGLT2 Inhibitors	dapagliflozin, empagliflozin, canagliflozin, ertugliflozin	low	Can skip on the day of a 24 h fast OR should skip if concern for dehydration exists	The dose can be skipped because there is no benefit to taking it and this would reduce healthcare costs to the patient.
GLP-1 Receptor Analogues, weekly	dulaglutide, albiglutide, semaglutide, exenatide-XR	low	None	
GLP-1 Receptor Analogues, daily	liraglutide, lixisenatide	low	None	For lixisenatide only, with a 24-h fast, can skip the dose
Alpha glucosidase inhibitors	acarbose, miglitol	low	Skip if patient not eating carbohydrates that meal	
Bile Acid Sequestrants	colesevelam	low	Skip	If the primary indication is for lowering cholesterol, dose should be taken
Dopamine Agonists	bromocriptine	low	None	
Basal Insulin (note: one study decreased basal insulin by 50% on fasting days and still had significant hypoglycemia rates [6], thus caution is required)	NPH, Levemin, glargine 1%, Basaglar	high	Take one-third of usual dose (67% lower dose) for controlled patient; take half of usual dose (50% lower dose) for uncontrolled patient	Definition of controlled and uncontrolled at the discretion of the treating physician based on risk for hypoglycemia. Monitor closely and proactively.
	glargine 3%, degludec	moderate	None initially	Monitor closely and proactively; reduce dose if fasting glucose goes below a pre-specified number

What is the Impact of Intermittent Fasting on Cardiovascular Health?

Table 3. Summary of studies employing intermittent fasting, with outcome data regarding lipid, blood pressure, and inflammatory markers.

Authors (Year)	Number Enrolled	Study Design/Fasting Protocol Used	Description of Participants	Study Duration	Effect on Lipids	Effect on BP	Effect on Inflammatory Markers
Harvie et al. (2011) [48]	107	RCT Intermittent energy restriction	Overweight or obese women (premenopausal)	6 months	↓TC ($p < 0.01$); NS: LDL, TGs, HDL	↓Systolic ($p = 0.99$); ↓Diastolic ($p = 0.84$)	
Varady et al. (2013) [40]	15	RCT Alternate day fasting	Individuals with BMI 20–29.9 kg/m ²	12 weeks	↓LDL ($p < 0.01$); ↓TGs ($p < 0.01$); NS: HDL	↓ ($p = 0.51$)	↓CRP ($p = 0.01$) ↓Leptin ($p = 0.03$) ↑Adiponectin ($p < 0.01$)
Bhutani et al. (2013) [39]	83	RCT Alternate day fasting plus endurance exercise (exercise control)	Individuals with obesity BMI 30–39.9 kg/m ²	12 weeks	↓LDL ($p < 0.05$); ↑HDL ($p < 0.05$); NS: TC, TGs	↓Systolic ($p = 0.254$); ↓Diastolic ($p = 0.570$)	NS CRP
Eshghinia et al. (2013) [41]	15	Observation over 8 weeks with alternating day fasting	Overweight or obese women BMI ≥ 25 kg/m ²	8 weeks	NS: LDL, TGs, HDL	↓Systolic ($p < 0.001$)	
Teng et al. (2013) [58]	28	RCT Fasting caloric restriction (300–500 cal/day) vs. control	Men in Malaysia BMI 23–29.9 kg/m ²	12 weeks	↓TC ($p < 0.001$) ↓LDL ($p < 0.05$) NS: HDL, TGs	↓Systolic ($p < 0.05$); ↓Diastolic ($p < 0.05$)	
Harvie et al. (2013) [49]	77	RCT Intermittent energy and carbohydrate restriction vs. control	Overweight or obese women	3 months	NS: LDL, TGs, HDL		NS: IL6, TNF α , leptin, adiponectin
Erdem et al. (2018) [59]	60	Prospective cohort (observational study)	Individuals from the Cappadocia cohort with prehypertension and hypertension (SBP 120–139 and ≥ 140 ; DBP 80–89 and ≥ 90 mmHg)	At least 1 week		↓Systolic ($p < 0.001$); ↓Diastolic ($p < 0.039$)	
Hoddy et al. (2016) [43]	59	8 week alternating day fasting Protocol	Obese individuals BMI 30–39.9 kg/m ²	8 weeks			↓Leptin ($p < 0.05$)

BP, blood pressure; CRP, C-reactive protein; NS: not statistically significant; RCT, randomized controlled trial; TG, triglycerides; TNF- α , tumor necrosis factor- α . ↑, increase. ↓, decreases.

1. Santos, H.O.; Macedo, R.C.O. Impact of intermittent fasting on the lipid profile: Assessment associated with diet and weight loss. Clin. Nutr. ESPEN 2018, 24, 14–21.
2. Vasim I, Majeed CN, DeBoer MD. Intermittent Fasting and Metabolic Health. Nutrients. 2022;14(3):631.

Caloric Restriction vs Time Restricted Eating (TRE)

- TRE has higher compliance and has shown promise in the improvement of metabolic risk factors, body composition, and weight loss in individuals[^]

[^] Anton SD, Moehl K, Donahoo WT, et al. Flipping the metabolic switch: understanding and applying the health benefits of fasting. *Obesity* (Silver Spring). 2018;26(2):254–68. Harvie M, Wright C, Pegington M, et al. The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss and metabolic disease risk markers in overweight women. *Br J Nutr*. 2013;110(8):1534–47. Varady KA, Bhutani S, Church EC, Klempel MC. Short-term modified alternate-day fasting: a novel dietary strategy for weight loss and cardioprotection in obese adults. *Am J Clin Nutr*. 2009;90(5):1138–43.

NUANCES OF INTERMITTENT FASTING (TIME RESTRICTED EATING)

Does the time for TRE matter?

- TRE schedules can vary
- Early time restricted eating has led:
 - Lower glucose and insulin levels
 - Increased LC3A (autophagy gene)
- Avoid food before bed led to lower cortisol and glucose levels

Early time restricted eating = Eating from 8 am to 2 pm

Source: Jamshed H, Beyl RA, Della Manna DL, Yang ES, Ravussin E, Peterson CM. Early Time-Restricted Feeding Improves 24-Hour Glucose Levels and Affects Markers of the Circadian Clock, Aging, and Autophagy in Humans. *Nutrients*. 2019 May 30;11(6):1234.

What should I eat?

- During the times when you're not eating, water and zero-calorie beverages such as black coffee and tea are allowed
 - Consuming any calories breaks a fast
- Gradually increase the duration and frequency of the fasting periods over the course of several months, instead of “going cold turkey”
- Patients should be advised that feeling hungry and irritable is common initially and usually passes after two weeks to a month as the body and brain become accustomed to the new habit

What are the best foods to break a fast with?

- Water
- What someone eats when they break a fast is not critically important
- Do not binge eat
- However, experts advise small portion meals, Mediterranean diet, avoiding added sugars and refined carbohydrates
- Cooked foods are easier to digest compared to raw foods

Intermittent Fasting is NOT Recommended For:

1. Children/Teens under age 18 yo
2. Pregnant/lactating women, or women who want to get pregnant
3. Adults of advanced age
4. Individuals with immunodeficiencies
5. Individuals with hypoglycemic events
6. People who suffer from eating disorders
7. Individuals with a body mass index below 18.5
8. People with Type 1 diabetes
9. Anyone with other medical conditions, particularly gout, or liver, kidney or heart disease should talk to their doctors in advance, as should anyone taking prescription medications

Risks Associated with TRE

-Mainly related to caloric restriction

- Hormonal imbalances in women
 - Changes/irregularity of menstrual cycles
- Osteoporosis
- Mood swings, fatigue
- Suppressed thyroid hormone conversion (weight plateau, low energy, constipation and hair loss)
- Activated stress response
- Hypoglycemia
- May increase the risk of gallstones

Note: Lightheadedness, dizziness, constipation, headaches and muscle cramps can result from fasting, especially early on before your body has gotten used to it.



INTERMITTENT FASTING: WHAT PCPS NEED TO KNOW



Intermittent fasting: What PCPs need to know

- Fully understand the specific mechanisms and beneficial effects of metabolic switching and cellular stress resistance
- Determine if it's safe for the patient
- Intermittent Fasting is not a first-line therapy for obesity, and is not for everyone
- Guidelines recommend promoting lifestyle changes and minimum of 150 minutes of moderate intensity physical activity on a weekly basis
- Start with small steps
 - Gradually introduce intermittent fasting
 - 12:12 (i.e., overnight fast from 7 pm to 7 am)
- Do not binge eat as a compensation for the caloric deficit associated with TRE
- What and how much you eat still matters
 - Educate patients regarding the importance of consuming nutrient-rich meals and adequate protein intake during feeding periods (i.e., Mediterranean diet)
 - TRE is more effective if combined with regular exercise and appropriate caloric restriction
- Adequate hydration during periods of fasting
- Getting adequate restful sleep and reduce/minimize stress in addition to diet and physical activity

Monitoring

Patients should be followed by a healthcare provider especially during the first 3 months of Intermittent Fasting

1. Adverse effects
2. Nutrient deficiencies: Vitamin and mineral levels
 - Vitamin D, vitamin B12, and electrolytes (i.e., salts)
3. Medications: Medications to control blood pressure, cholesterol and glucose should be monitored and may need to be reduced if the patient loses weight
4. Therapy: Patients should participate in behavioral change programs to help achieve long-term weight management

Summary

- We all want to live longer and better
- When you eat is as important as what and how much you eat
- Intermittent Fasting is a concept/tool, not a specific diet
 - TRE is the most common type of intermittent fasting (schedules vary)
 - There isn't sufficient evidence to support a fasting protocol for any disease; and is not recommended for everyone
- IF has mild/modest weight loss potential (4%-8%)
- IF is more effective if combined with regular exercise and appropriate caloric restriction
- TRE improves health by:
 - Leveraging changes in metabolism (**metabolic switch**)
 - Initiating cellular repair processes (**autophagy**)
 - Increases insulin sensitivity
 - Reduce cell damage from inflammation and oxidation
- Ask yourself: "What is the risk of doing the intervention vs the risk of NOT doing the intervention?"
 - If the risk of doing the TRE is not high, experimenting with it may not be a bad idea.



Appendix

Intermittent fasting apps (on iPhone and Android):

1. Zero: can be customized to track fasting times.
2. Bodyfast: coaching and meal planning tips.
3. Fastic: includes 400 recipe ideas.
4. Fastient: track fasting times and monitor diet.
5. Vora: daily fasting, goal timing, weight loss progress, and community support.
6. More

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