Intermittent Fasting: Fast or Fad: The Science behind today's fasting Regimens

Sangeeta Pradhan, RD, LDN, CDCES

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Objectives

• Review the metabolic and cellular responses to starvation and intermittent fasting.
• State the most studied intermittent fasting regimens.
• Summarize the studies in animal models.
• Review the outcomes from preclinical and clinical studies on intermittent-fasting regimens in healthy persons and in patients with metabolic disorders.
• Review the safety and efficacy of today's intermittent fasting regimens.
• State why RDs must and should stay on the leading edge of this research to get their patients to eat healthfully.

Metabolism of fasting

Energy substrates used and metabolic changes

Metabolic adaptations to IF

Brain switches to ketones for fuel during starvation

Which hormones are triggered when we eat?

Brain switches to ketones for fuel during starvation

• Ketone bodies as a fuel for the brain during starvation

Source: Oliver E. Owen, Biochemistry and Molecular Biology Education Volume 33, Issue 4, First published: 03 November 2006

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Which hormones are triggered when we fast?

- Nutrient scarcity (fasting)
- Growth is inhibited
- Glucagon

Catabolism

- Insulin suppression
- Lack of growth factors
- Recycling of waste
- Protective mode
- Repair and clean up

Longevity

When less is more: Fasting physiology is ingrained in our genome

- Nutrient deprivation increases longevity
- Yeasts deprived of nutrients will arrest growth
- Acetate: "Alternate metabolic program" - metabolic switch to ketones
- Evolved billions of years ago in prokaryotes in hostile environments
- Repeated exposure to fasting: Lasting adaptive protective responses in mammals today

Fasting activates protective effects and extends lifespans of yeast, worms and mice:

Source: Longo, Mattson, Cell Metabolism 2014

IF and calorie restriction: Building the cell's arsenal

- Brain cell regeneration
- Adaptation stress response
- Enhanced mitochondrial health
- Dna repair

Ketones: Not just fuel, but “Miracle Molecules”??

- Potent signaling molecules
- Key role in aging and homeostasis
- Inhibit tumor growth
- Prevent neuronal injury and death caused by free radicals
- Mediate shift from excitatory to inhibitory neurotransmitters: reduced seizure activity
- Upregulates transcription of antioxidant genes
Cascade effect from excess glucose/energy intake (IF and CR or calorie restriction reverse this effect)

- Increased glucose
- Hyperinsulinemia
- Upregulation of growth hormone receptor
- Increased free IGF-1
- Increased Mtor and growth activation
- Decreased IGF binding protein

Hursting et al., Cancer Metab. 2013; 1: 10

What’s MTOR??
MTOR what??!!

Mtor: Master regulator of cell growth, increases protein synthesis, signals the body to “build”...

- MTOR is an enzyme: a kinase that transfers a phosphate group from ATP to a substrate
- Senses environmental, cellular nutrient status, turns up the heat
- Stimulates protein synthesis, cell growth, proliferation, angiogenesis
- Activated by growth factors, nutrients, insulin and mitogens
- Deactivated by a nutrient or energy deficit (CR or fasting)
- Dysregulated in cancer and T2DM
- Too much MTOR activation can lead to obesity, T2DM and cancer
- Suppresses autophagy

What is MTOR? (What would cells need, to turn on growth pathways?)

- AMP activated kinase; Under what conditions would cells have large amounts of this enzyme?

- Energy deprivation (fasting) triggers cells to hydrolyze ATP to obtain energy
- ATP hydrolysis or breakdown, creates AMP
- Large amounts of AMP accumulate in the cell
- Activates “AMP activated kinase”, fuel sensor, mobilizes the body’s back-up fuel
- Shuts down growth pathways by inhibiting MTOR → autophagy
AMP activated kinase

How does dietary restriction or fasting modulate autophagy and cancer therapy?

- Decreased ATP/Increased AMP in cells
- High intensity exercise
- Nutrient scarcity/Starvation/catabolism
- Low growth factor levels
- Decreased IGF-
- Activated AMP kinase
- Inhibition of MTor
- Inhibition of growth
- Catabolism

Mechanisms that extend life and health span

- Absence of glucose
- Absence of amino acids
- Inactivate growth signaling (MTor)
- Stress resistance transcription factors
- Stress resistant, antioxidant genes
- Fasting and DER (Protect DNA)
- Overall increased stress resistance

Calorie restriction and metabolic pathways affecting cancer

- Insulin/IGF-1, Leptin
- Decreased glucose-Warburg effect
- Decreased cell proliferation
- Increased AMPK
- Decreased MTOR
- Autophagy (repair)

Nutrient sensors determine if catabolic or anabolic pathways are followed at any given time

- AMPK (nutrient sensor)
- Glucagon
- Catabolism
- Autophagy
- Mtor (nutrient sensor)
- Growth/Anabolism
- Insulin
- IGF-1

Autophagy and intermittent fasting: the connection for cancer therapy

- Converts cellular debris and dysfunctional organelles into energy and recycles waste
- Autophagy is an evolutionarily conserved lysosomal catabolic process
- Dysfunctional autophagy contributes to many diseases, including cancer
- Nutritional restriction is a promising protocol to modulate autophagy and enhance the efficacy of anticancer therapies while protecting normal cells.

IF, Ketones, the Warburg effect and cancer therapy

- An increase in the rate of glucose uptake and preferential production of lactate, even in the presence of oxygen
- Cancer cells are obligate glucose users
- Production of ketones then starves cancer cells
- Non cancer cells can utilize ketones effectively as a fuel source
- Decreased IGF-1, decrease in growth signaling pathways
Autophagy or cellular cleansing: what inhibits, and what activates this process, and why?

Key: Green arrows: activation
Red: inhibition

Autophagy

AMPK
Low insulin/glucagon ratio
Intense exercise
MTOR
High nutrient intake

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Abort Autophagy: Gotta eat!!!

2 major forms of IF in animals

Alternate Daily Fasting (ADF)
Time restricted Fasting (TRF)

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Time restricted feeding helps prevent or reverse metabolic diseases in mice fed a high fat diet

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Animal studies

- Mice maintained on ADF have better running endurance than mice that eat ad lib
- Balance and coordination are also improved in animals on daily TRF or ADF
- IF enhances spatial, associative and working memory
- IER superior to CER wrt to longevity and certain cancers
ADF vs CER (Continuous Energy Restriction) in mice

- Greater LBM/fat mass ratio on ADF vs 30-40% CER diet
- Improved glucose and fatty acid metabolism (increased β-hydroxybutyrate levels) in ADF vs 40% CER
- Greater reduction in heart rate and BP compared to 40% CER

- Conflicting evidence with longer term studies
  - Rats maintained on an ADF x 1 month had improved glucose tolerance
  - Rats maintained on an ADF x 8 month had impaired glucose tolerance

The 3 most commonly studied fasting regimens, (there are various others)

1. Alternate-day fasting regimen
   - Day 1: Regular
   - Day 2: Fasting
   - Day 3: Regular
   - Day 4: Fasting
   - Day 5: Regular
   - Day 6: Fasting
   - Day 7: Regular

2. 5:2 IF regimen
   - Day 1: Regular
   - Day 2: Fasting
   - Day 3: Regular
   - Day 4: Fasting
   - Day 5: Regular
   - Day 6: Fasting
   - Day 7: Regular

3. Time restricted feeding
   - Limits food intake to 10 hours, followed by 14 hours of fasting
   - Midday TRF superior to late-day TRF, insulin sensitivity highest in am

Diseases with benefits: IF in humans

- Insulin resistance
- Dyslipidemia
- HTN
- Inflammation
- Increased stress resistance

Disruption of the circadian regulation of hormones with disrupted eating can lead to metabolic disorders: Time restricted feeding or TRF can offset this

- SCN: Suprachiasmatic nucleus in hypothalamus
  - Master clock in the brain

- Syncing eating pattern with the body’s circadian rhythm resets your biological clock, enhancing metabolism

What is Time restricted feeding or TRF: human studies

- Limits food intake to ≤10 hours, followed by ≥14-hour fast
- Done w/o weight loss
  - Limits food intake to ≤10 hours, followed by ≥14-hour fast

- Glucose, lipid, energy metabolism regulated by circadian rhythm

Are the benefits of IF related to weight loss or independent from weight loss?
First rigorous RCT in men with prediabetes: combining IF with circadian rhythms-eTRF

- eTRF
- 6 hour eating window
- Dinner before 3 pm
- 12-hour control group
- 5 weeks
- Washout period of 7 weeks
- Improved insulin levels
- Improved β cell responsiveness
- Improved Oxidative stress
- Improved CVD markers
- Independent of food intake and wt loss

Sutton et al, Cell Metabolism, 2018

Standard American Diet (SAD), ADF or TRF

- Ketones are elevated during the last 6-8 h of the 18 h fasting period in Section C in adjoining figure or TRF


ADF

- Most studied IF: Alternate days of 70% CR.
  - 3-7% weight reduction
  - 3-5.5 kg body fat reduction
  - 10-12% reduction in serum cholesterol
  - Reduction in TGs Improvement in glucose homeostasis
- Limitation: No CER (Continuous energy restriction) comparator, hence unclear if benefits were from weight loss or specific effect exclusively seen from IF

ADF in Normal individuals:

- 3 weeks of ADF resulted in reductions in body fat and insulin levels in normal weight men and women.
- In one study1, alternate-day fasting was effective for weight loss and cardio-protection in normal-weight and overweight individuals
- Improvements in cardiovascular health indicators seen within 2 to 4 weeks after ADF initiation
- Improvements dissipate over a period of several weeks after resumption of a normal diet.2

Varady et al, Nut J 2013
Vander et al, J Physiol 2016

30 healthy participants on ADF for 22 days lost 4.5 % wt, 4% fat mass and 51% drop in insulin levels.

Consistent with results in mice, some IF diets do not adversely affect and might enhance physical performance

Parallel studies in animals showing improved glucose metabolism without changing weight

How does ADF affect normal individuals?

4 weeks of strict Alternate day fasting in healthy middle-aged humans

- 37% calorie reduction on average.
- No adverse effects occurred even after >6 months.
- ADF reduced trunk fat, improving the fat-to-lean ratio, and increased ketones even on non-fasting days.
- Reduced LDL and other inflammatory markers noted.
- Results support the safety of ADF.
- More comprehensive studies needed before ADF becomes a clinically relevant intervention.

Stikovic et al, Cell Metabolism, 2019
PF VS CER

- Calorie restriction
- CER is a sustained reduced intake of usually around 30% fewer calories than baseline
- Improves metabolism and increases stress response genes, like IF
- One phase only, unlike IF
- Hunger is less pronounced
- Greater adherence

- Periodic fasting (PF)
- PF creates a more extreme deficit but for only a short duration
- Improves metabolism and increases stress response genes
- 2 distinct phases: During the acute deficit, stem cells are activated, during re-feeding, systems can regenerate
- Ketones bodies and autophagy
- Intense hunger, decreased adherence

Testing the safety and tolerability of a zero calorie ADF with CER

Randomized to
Zero kcal ADF x 8 weeks
No significant difference
After 24 weeks, lost fat mass, gained LBM
No adverse effects seen

Randomized to
CR of -400 kcal/day x 8 weeks
At 8 weeks no significant difference
After 24 weeks, gained both fat mass and LBM

Adults with obesity (BMI ≥30 kg/m², age 18-55)
No differences in weight, body composition, lipids or insulin sensitivity at 8 weeks
After 24 weeks of unsupervised weight regain
Changes from baseline in % fat mass and lean mass were more favorable for ADF
Both groups lost weight
There was no difference in weight regain at 24 weeks.

Victoria A. Catenaccio et al., Obesity Silver Spring, 2016

IECR (Intermittent energy and carb restriction) vs Daily energy restriction (DER)

< 40 gms carbs/day x 2 days/wk in 1 IECR

Randomized to
Ad lib protein and fat in the second IECR (5:2)

• Randomized to

• Randomized to

Limited published RCTs in humans

• 2 consecutive days of 55-70% CR every week
• 4 days of 50% CR each week
• Equivalent wt. loss between IF and CR

Long term RCT with 100 obese adults

• ADF did not produce superior adherence to wt management or cardio-protection vs continuous energy restriction, CER

Long-term effects of calorie or protein restriction on serum IGF-1 concentration in humans
Low IGF-1 and glucose levels induced by fasting is protective to cells
Variable effects on IGF-1 seen in different studies

Fasting: Low IGF-1 and low glucose
- Protective
- Tumor prevention
- Reduction of growth hormone signaling

In mice and men

Variable effects on IGF-1 seen in different studies

2 large vs several small meals in pts w/DM

- 24-week randomized, cross-over trial
- 54 patients w/T2DM
- 2 regimens, 12 weeks each
  - Breakfast and lunch only vs
    - 6 meals a day.
- Both regimens had the same macronutrient and energy content
- Further, larger scale, long-term studies needed before offering recommendations re: meal frequency.

Safety considerations

- Do not use with the following populations as studies have not be done:
  - Children
  - The Elderly
  - Contraindicated in:
    - Anyone with a low BMI/Eating disorders
    - Pregnant/breast feeding
    - People with advanced diabetes on medications or other medical conditions
    - Fasting >24 hours and those lasting 3 or > days must be done under medical supervision, including water fasts

Psychological effects of IF

- IE: “Don’t set any rules around food and instead connect with your own innate hunger and satiety cues”
- Flies in the face of intuitive eating principles and following one’s hunger cues by eating only within a restricted time window
- Not recommended for anyone with an eating disorder as it could get people fixated on food and timing
- RDs argue that people might overeat on feeding days, but the studies show that they don’t

IF and cancer rates in humans

- Limited data on IF and cancer rates in humans
- Indirect evidence on cancer risk biomarkers: insulin, cytokines, inflammation related molecules: leptin and adiponectin
- In a cohort of 3088 patients*, fasting < 13 hours per night was linked w/ a 36% increase in the risk of breast cancer recurrence compared with fasting > 13 or more hours per night
- Several case studies involving patients with glioblastoma: IF can suppress tumor growth and extend survival.

WHEL’s study

3/13/2021

Of concern.. prolonged fasts

- Long term effects of prolonged fasts on BMR, how quickly does it rebound
- Nitrogen (protein) losses
- Mineral losses with fasting: the notoriety of fasting
- Decreased plasma volume, loss of K and Mg along with Na
- With IF, repletion of minerals is key during fed days
- In an RCT despite medication reduction, fasting increased the risk of hypoglycemia
- Refeeding
- Careful monitoring
What do we know so far?

- Almost any intermittent fasting regimen can result in some weight loss. 84% of the intervention trials in the AND1 systematic review reported significant wt. loss.
- No harmful effects of intermittent fasting have been reported in studies in healthy adults.
- Not clear that periods of fasting (i.e., hunger) necessarily lead to periods of overeating.
- Circadian rhythm eating = healthy eating may be a viable strategy for wt. loss
- Prolonged nightly fasting may be a simple, feasible, and potentially effective disease prevention strategy at the population level.
- Overall, IF at least short term, may provide better outcomes than daily continuous diet restriction for health and potentially for weight loss, with preservation of fat free mass
- Very recent systematic review and metaanalysis2 IF significantly:
  - Improved glucose control and insulin resistance
  - A decrease in leptin level,
  - An increase in adiponectin concentration w/out chronic disease
- Future studies should incorporate objective measures:
- Data are lacking regarding the effects of intermittent fasting on other health behaviors such as sleep, and
- Previous meta:
- With a reduction in BMI,
- will help assess if behavioral and metabolic changes are sustainable
- Whether they have any long
- Important for establishing diet recommendations for the general population including the population with
- Most studies utilized
- Not clear that periods of fasting (i.e., hunger) necessarily lead to periods of overeating.
- Recommendations for dietary behavior on non
- Enroll diverse populations who disproportionately experience obesity and related health maladies.
- The number of fasting days per week,
- Insufficient data to determine
- Whether they have any long
- Systematic adaptations to bioenergetic
- Points to ponder..
- Limited long-term research, backed by AHA statement
- Most studies utilized small sample sizes of participants.
- Previous meta-analysis on the glucoregulatory effect of an IF have also shown conflicting results.
- Important for establishing diet recommendations for the general population including the population with obesity or prediabetes.
- Data are lacking regarding the effects of intermittent fasting on other health behaviors such as sleep, and physical activity
- Insufficient data to determine
  - The optimal fasting regimen, including the length of the fasting interval
  - The number of fasting days per week
  - The degree of energy restriction needed on fasting days,
  - Recommendations for dietary behavior on non-fasting days

Fast or a fad that will fade like other “diets”??

- Cannot meet all your nutrient needs in one meal
- Disagreement even among researchers on IF benefits and which type of IF would be optimal
- Excessive hunger on fasting days; adherence was an issue in IF vs CER
- Studies done in mainly young or middle-aged participants – outcomes cannot be extrapolated to other age groups

Points to ponder..

- 3 meals and snacks ingrained in our culture, which might pose a formidable barrier to future implementation efforts.
- Large scale, rigorous, randomized trials of intermittent fasting regimens in free-living adults are needed and should last for at least a year
- Will help assess if behavioral and metabolic changes are sustainable
- Whether they have any long-term effect on biomarkers of aging and longevity
- Future studies should incorporate objective measures:
  - Energy intake, sleep, and energy expenditure
  - Assess numerous markers of disease risk and
  - Enroll diverse populations who disproportionately experience obesity and related health maladies.
- Adapted from:
- J Clin Med 381;26 nejm.org December 26, 2019

Appendix: Adapted from Effects of Intermittent Fasting on Health and Aging

1. Patterson et al, Journal of the Academy of Nutrition and Dietetics, August 2015

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Appendix: Sample prescriptions: Source: Effects of Intermittent fasting

<table>
<thead>
<tr>
<th>Month</th>
<th>Time restricted feeding</th>
<th>5:2 Intermittent feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1</td>
<td>10 hr feeding 5 days/week</td>
<td>1000 calories 1 day/week</td>
</tr>
<tr>
<td>Month 2</td>
<td>8 hr feeding 5 days/week</td>
<td>1000 calories 2 days/week</td>
</tr>
<tr>
<td>Month 3</td>
<td>6 hr feeding 5 days/week</td>
<td>750 calories 2 days/week</td>
</tr>
<tr>
<td>Month 4</td>
<td>6 hr feeding 7 days/week</td>
<td>500 calories 2 days/week</td>
</tr>
</tbody>
</table>

Source: n engl j med 381:26 nejm.org

December 26, 2019

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