Fast-Mimicking Diets
Therapy to Combat the Relentless Effects of Aging

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OBJECTIVES

Aging & Biological Pathways

Chronic Conditions: A Growing Problem
Evolution of Growth & Aging Pathways
Dietary Intervention

Fasting’s Impact on Aging
Fasting Mimicking
Prevention & Disease Management
Clinical Applications
People are living longer lives than ever before
People over 65 will comprise more than 22% of the population by 2030
Age-associated chronic diseases & conditions are also increasing

(US Census National Population Projections 2012
CDC, National Center for Health Statistics, National Health Interview Survey
CDC, National Center for Chronic Disease Prevention & Health Promotion 2012)
Cancer, aging, obesity & chronic diseases: growing epidemics with few answers

- **86%** of our nation’s healthcare costs are spent treating people with chronic diseases.
- **70%** of all Americans are overweight or obese.
- **100+ million** Americans are projected to be diabetic by 2050.
- **130+ million** Americans are affected by chronic diseases, that’s 40% of the population!
- **70 million** Americans have hypertension with elevated risk for stroke and heart attack!
- **> 1 billion** people worldwide are over 65 years old
- **8.2+ million** people die annually of cancer worldwide, making it the leading cause of death.

People worldwide are over 65 years old

Americans are affected by chronic diseases, that’s 40% of the population!

Americans have hypertension with elevated risk for stroke and heart attack!
Aging & chronic conditions

Why don't young people get Alzheimer’s, Diabetes, Cancer, Cardiovascular Disease, or Stroke?

• Because AGING is the catalyst for these diseases
• 67-87% of us will die of one of these diseases

Leading Causes of Death 2014

- Heart disease: 614,348 (23.4%)
- Cancer: 591,699 (22.5%)
- COPD: 147,101 (5.6%)
- Accidents: 136,053 (5.2%)
- Stroke: 133,103 (5.1%)
- Alzheimer's: 93,541 (3.6%)
- Diabetes: 76,488 (2.9%)
- Flu, pneumonia: 55,227 (2.1%)
- Kidney disease: 48,146 (1.8%)
- Suicide: 42,773 (1.6%)

Source: Center for Disease Control & Prevention

AGING → multiple forms of damage in different tissues as a result of failure of cellular maintenance pathways
Aging & Biological Pathways

An Increasing Problem:

- Age-associated diseases are an enormous challenge & financial burden globally

Average life expectancy has increased dramatically in the last 100 years. Healthy life expectancy ("healthspan") has not increased equivalently.

- Aging is regulated by Nutrient Sensing Pathways
  
  Targets for nutritional & pharmacological intervention that may *increase longevity & healthspan*

(Christensen et al., 2009, Hung et al., 2011)
So - should we treat aging?
Aging & Biological Pathways
Can a Diet That Mimics Fasting Turn Back the Clock?

Jennifer Abbasi
Starved organisms live longer

Bacteria

Fed
Starved

Baker’s Yeast

Fed
Starve

Worms

Fed
Starved

BBC Nature News June 2014: Worms live longer when they stop eating
Continuous eating has led to unhealthy aging & early onset of chronic diseases: cancer, Alzheimer’s, diabetes & cardio-vascular diseases
In the Distant Past, Food was Scarce:

- Dependent on the hunt and the harvest
- Hunger punctuated by intermittent bursts of eating
- These patterns forced strong evolutionary pressures on the body’s ability to survive during periods of hunger or fasting.
Dietary Interventions That Affect Aging & Healthspan
Fasting: an integral part of healthy human diet, lost...

Due to food scarcity, **Fasting** was part of the Human Diet for 99% of our evolution on Earth.

Fasting was then sustained by major 5 religions. Fasting was replaced in last 50 years by patterns of uninterrupted, daily food intake.
Fasting: To abstain from food

Biological Fasting: To not consume food that triggers cellular food sensing pathways: PKA, RAS & mTOR. The sensing pathways are triggered up to 24h after the last meal. So biological fasting starts 24h from last meal

Misconceptions: Juice fasting is fasting because it does not contain solid food

Time Restricted Eating: No eating for 12 or 16 hours - not biological fasting
Evolution of fasting

Fasting is actually accompanied by an increase in activity and energy

- When hungry, the body is programmed to increase activity to seek nourishment
- In contrast, the body is sedentary when satiated
- Increased energy accompanied by protection from disease and deleterious aging – fasting is truly the miracle “drug”
When food is scarce the body acts to conserve energy by diminishing cellular growth pathways by regulating IGF-1, TOR and PKA (key nutrient sensing pathways), resulting in:

- Increased cellular maintenance and protection
- Increased activation of stress resistance pathways
- Removal and replacement of damaged/dysfunctional cells
- Reduction of inflammation.

Fasting challenges the body, which engages stress response pathways to increase chance of survival.
### How fasting works

<table>
<thead>
<tr>
<th>Time Restricted Eating (TRE) and Intermittent Fasting</th>
<th>Prolonged Fasting</th>
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<td>• Few Hours: typically 12-24 hours</td>
<td>• &gt;3 days, typically 5 days</td>
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<tr>
<td>• Counterbalance the previous Feeding Period</td>
<td>• Induces cellular effects</td>
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<td>• Maintains Healthy Weight</td>
<td>• Autophagy (Nobel Prize in Medicine, 2016)</td>
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<td>• Maintains Healthy Metabolism</td>
<td>• Stem Cell Based Regeneration</td>
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#### Benefits

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#### Issues

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#### Solutions

- **Fasting Mimicking Meal for Healthy TRE**
- **Fasting Mimicking Diet**
Fasting is all about timing of calorie intake, food restriction, or both

Intermittent Fasting – cyclical fasting in intervals

Examples of types of fasting

**Time-restricted eating (TRE) – daily**

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<tr>
<th>Sunday</th>
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**Alternate day fasting**

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**5:2 fasting – weekly**

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**Prolonged Fasting – fasting days in a row**

**Periodic fasting – Fasting Mimicking Diet (FMD)® few times/year**

**Key:**

- **Fasting**
- **Non-fasting**
The body identifies the presence of food through nutrient-sensing pathways

- IGF-1, MTOR, and PKA are 3 key nutrient-sensing pathways
- Nutrient-Sensing Pathways: pro-growth, pro-aging, lead to many common health problems including heart disease and cancer

Fasting down-regulates these pathways
What are the nutrient sensing pathways on the cells?

RAS & PKA: Carbohydrate-Insulin pathway

mTOR: Protein-IGF pathway

Wei et al., 2008; Cheng et al., 2014
Fasting Mimicking

Fasting Mimicking Diets (FMDs)
downregulate the body’s key nutrient-sensing pathways, while still providing needed nourishment.

Using a specific combo of low protein, carbohydrates and sugars, and high fat, FMDs shuttle food into the body without releasing the signaling factors for cellular growth & aging.

In other words, FMDs allow you to eat but trick the body into acting like it is fasting.

**The stomach sees food, while the cells see fasting**
What is the Fasting Mimicking Diet?

- Macronutrients: high good fat, low in protein, low in Carbs (66 ingredients carefully studied to nourish while not triggering the nutrient sensing pathways) + Minerals & Vitamins
- Comes in a box with food for 5 days soups, bars, crackers, drinks, teas, supplements
- Plant Based, Natural ingredients
- GRAS by FDA
- Scientifically Developed and Clinically Tested at USC, Mayo Clinic, U of Genoa, IFOM, etc.
- Funded by NIH and EU grants: more than $45MM
- Effective in initial trials against Aging and Multiple Chronic Diseases
Fasting Mimicking Diet: The Only Patent In History Awarded on Regeneration & Longevity


Promoting Tissue/Organ Regeneration, Longevity and Healthspan

https://patents.justia.com/patent/10015980
Pre-clinical & Clinical Trial –
Aging, Longevity & Metabolic Health
Breakthrough Discoveries Published in top Scientific & Medical Journals

Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease

Sebastian Brandhorst,1,6 Mahshid Shlebehchi,1 Hamed Mirzaei,1 Chia Wei Cheng,1 Julia Budnai,1 Susan Groschen,2 Wendy J. Mack,2 Esra Guen,1 Stefano Di Biase,1 Pinchas Cohen,1 Todd E. Morgan,1 Tanya Dorff,3 Kurt Hong,4 Andreas Michalsen,5 Alessandro Laviano,6 Valter D. Longo1,7

Calorie restriction or changes in dietary composition can enhance healthy aging, but the inability of most subjects to adhere to chronic and extreme diets, as well as potentially adverse effects, limits their application. We randomized 100 generally healthy participants from the United States into two study arms and tested the effects of a fasting-mimicking diet (FMD)—low in calories, sugars, and protein but high in unsaturated fats—on markers/risk factors associated with aging and age-related diseases. We compared subjects who followed 3 months of an unrestricted diet to subjects who consumed the FMD for 5 consecutive days per month for 3 months. Three FMD cycles reduced body weight, trunk, and total body fat; lowered blood pressure; and decreased insulin-like growth factor 1 (IGF-1). No serious adverse effects were reported. After 3 months, control diet subjects were crossed over to the FMD program, resulting in a total of 71 subjects completing three FMD cycles. A post hoc analysis of subjects from both FMD arms showed that body mass index, blood pressure, fasting glucose, IGF-1, triglycerides, total and low-density lipoprotein cholesterol, and C-reactive protein were more beneficially affected in participants at risk for disease than in subjects who were not at risk. Thus, cycles of a 5-day FMD are safe, feasible, and effective in reducing markers/risk factors for aging and age-related diseases. Larger studies in patients with diagnosed diseases or selected on the basis of risk factors are warranted to confirm the effect of the FMD on disease prevention and treatment.
The Biological Effects of FMD

Day 1
Fasting State
• Primes the body to transition in a fasting state and begin cellular optimization

Day 2
Fat Burning
• The body switches to fat burning mode.
• Cellular recycling and clean up (autophagy) begins

Day 3
Cellular Autophagy*
• Autophagy Continues
• Most people reach full ketosis

*Awarded Nobel Prize of Medicine 2016

Day 4
Cell Regeneration
• Autophagy continues and stem-cell regeneration starts

Day 5
Regeneration Continues
• Stem-cell based regeneration continues
• The body is being rejuvenated from within
Prolonged fasting with FMD promotes cellular regeneration to improve body composition.

72 hours of continuous fasting promotes stem-cell activation and cellular regeneration. Preclinically, it induces 93.7% in stem cell production.

Autophagy plays the key role in the cell rejuvenation process while fasting.
FMD Clinical Trial Results – Longevity, Weight and Metabolic Health

Participants lost an average of 5 lbs (Fig. 1) coming mostly from abdominal fat shown as reduction in abdominal fat mass (Fig. 2) and >1-inch loss in waist circumference (Fig. 3) while preserving lean body mass (Fig. 4). IGF-1, a marker associated with increased mortality and DNA damage in human cells, was reduced by 14% (Fig. 5).

Blood pressure (BP) was significantly reduced from 117.4 to 113.6 mm Hg (systolic) and 75.7 to 72.8 mm Hg (diastolic) (Fig. 6 & 7). Total cholesterol was reduced nearly 10 mg/dL with significant reductions of LDL from 104.9 to 99.2 mg/dL (Fig. 8). C-reactive protein (CRP) levels decreased from 1.5 mg/L to 1.0 mg/L after participants had resumed their normal diet for 5 – 8 days after cycle 3 (Fig. 9). A transient, major and significant elevation of stem cell/regenerative markers was also observed (Fig. 10).
More significant results for the group of individuals who had elevated health risks

FMD Clinical Trial Results – Longevity, Weight and Metabolic Health

In obese participants (BMI>30), body weight decreased 9 lbs (Fig. 1). Weight remained significantly lower after subjects returned to their normal diet for an average of 3 months. In overweight participants (BMI>20), abdominal fat was reduced by >7% (Fig. 2) with preserved relative lean body mass and decreased waist circumference by approximately >3 cm (Fig. 3). In participants with high cholesterol (>195 mg/dL), total cholesterol was reduced by 29 mg/dL and LDL-cholesterol reduced by 15 mg/dL (Fig. 4). In participants with high triglycerides (>100 mg/dL), triglyceride levels were reduced by >25 mg/dL (Fig. 5).

Blood pressure (>120/80) systolic and diastolic BPs were reduced by >6 mmHg (Fig. 6). Blood pressure remained significantly reduced after subjects returned to their normal diet for an average of 3 months. In high fasting glucose participants (>159 mg/dL), fasting glucose was reduced by >10 mg/dL (Fig. 7) and remained reduced after subjects returned to their normal diet for an average of 3 months; in low glucose participants (<99 mg/dL), fasting glucose remained unchanged (Fig. 7). IGF-1, was reduced by 20% in participants with high IGF-1 levels (Fig. 8). In participants at an average risk for developing cardiovascular disease (CRP-reactive protein between 1-3 mg/L), CRP was lowered >1 mg/L closer to the lowest risk range (Fig. 9).
Health benefits of fasting

**Time-Restricted Eating (TRE) and FMD**

- **Glucose Insulin, IGF-1**: To maintain healthy levels
- **Cholesterol, Blood Pressure**: To maintain healthy levels
- **C-Reactive Protein (CRP) Inflammation**: To maintain healthy levels
- **Weight & Abdominal Fat**: Reduced

**Fast to Performance**

- **Preserved**
  - Lean Body Mass
  - Bone density and muscle mass
- **Increased**
  - Stem Cells
  - Rejuvenation (fasting mimicking technology)

**FMD Periodic Fasting Only**

- To maintain healthy levels
- To maintain healthy levels
- Reduced
Fasting and healthy weight loss

FMD is clinically proven to help individuals with normal-BMI reading to lose an average of 5.2lbs of fat and 1.2 inches off waist circumference, while overweight/obese may lose >8lbs, mainly with visceral fat reduction while protecting Lean Body Mass:

The FMD resulted in a 3% reduction in BW that remained lower even after refeeding.
FMD pre-clinical trial on diabetes

Reversing Diabetes via Pancreatic Stem Cell Regeneration

Preclinical

Type 1 diabetes (STZ model)

Type 2 diabetes, T2D (genetic model)

FMD attenuates hyper-glycemia

FMD reverses pancreatic β-cell failure – insulin production restored

Cheng et al. Cell, February 23, 2017
Fasting Mimicking Diet: A unique patent on treating diabetes


Fasting condition as dietary treatment of diabetes

https://patents.justia.com/patent/9386790
FMD preclinical trial on cancer
Intercepting Cancer in Conjunction with and In Between Current Treatment Options

Preclinical Results Below. Human Trial expected to be completed in Mid-2019

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

Graphical Abstract

Authors
Stefano Di Biase, Changhan Lee, Sebastian Brandhorst, ..., Min Wei, Todd E. Morgan, Vlado D. Longo

Correspondence
vlongo@usc.edu

In Brief
Di Biase et al. show that combining a fasting-mimicking diet with chemotherapy increases the levels of bone marrow common lymphoid progenitor cells and cytotoxic CD8+ tumor-infiltrating lymphocytes, delaying tumor progression. In breast tumors, this effect is partially mediated by downregulating HO-1.
The top eating pattern cited was intermittent fasting (10 percent). Diets considered at least somewhat restrictive of carbohydrates were well-represented, including Paleo (7 percent), low-carb (5 percent), Whole30 (5 percent), high-protein (4 percent), and ketogenic/high-fat (3 percent).
Fasting Mimicking Diet (FMD) started at middle age reverses the effect of aging on white blood cell number.

FMD activates blood stem cells resulting in regeneration and rejuvenation of the immune system.

Periodic Fasting Mimicking Diet (FMD) Started at Middle Age Extends Longevity

Mice placed on a 4 day FMD twice a month starting at 16 month of age

Fasting Mimicking Diet cycles reduce & delay cancer

Mice placed on a 4 day FMD twice a month starting at 16 month of age

All Tumors

Increased cancer-free rates in mice

- Multiple fasting cycles + chemotherapy promote cancer free survival in 35-55% of mice with human lung adenocarcinoma and mesothelioma xenografts

FMD™s and Neuro-cognition

Improves cognitive performance in mice
FMDs & Neurogenesis

FMD™s Improve neurogenesis


Demonstration of re-growth of new cells in mouse models:

Bromodeoxyuridine (BrdU) &
FMD Autoimmune

Reduces autoimmunity & alleviates MS symptoms

- Weekly cycles of FMD are effective in ameliorating cellular and disability measures in mice
- FMD reduced clinical severity in all mice, and caused complete recovery in 20% of the animals

Choi, Y et al. Cell Reports 2016
Regenerates damaged nerve tissue

- FMD promoted oligodendrocyte precursor cell regeneration and re-myelination in axons in mice

Choi, Y et al. Cell Reports 2016
FMD preclinical trial on Multiple Sclerosis
Reversing/Intercepting Auto-Immune Diseases: Multiple Sclerosis
Preclinical Results

FMD promoted oligodendrocyte precursor cell regeneration and re-myelination in axons in mice
Rejuvenation from within – periodic FMD is more effective in at risk patients

Blood glucose drops in pre-diabetic patients after 3 cycles of the FMD

IGF-1, associated with aging and cancer, is reduced after 3 cycles of the FMD
CRP, a risk factor for cardiovascular disease, is reduced after 3 cycles of the FMD

Circulating stem cells in humans undergoing FMD cycles

Rejuvenation from within

Periodic Fasting Mimicking Diet

Reduction in age-related disease
- Diabetes
- Cancer
- CVD
- Alzheimer’s

Disease Risk

Diet

Aging

Toxins
Look Backwards to Provide the Solutions for Optimal Longevity and HealthSpan

Thank you for your kind attention!

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@DrFeliceGersh


Bibliography


Brandhorst S, et al., A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan; Cell Metabolism 22, 1–14; July 7, 2015