Calorie Restriction, Longevity and Muscle Function: Emerging Research and Clinical Considerations

TODAY’S AGENDA:
- Introduction & Housekeeping
- Speaker Introduction
- Presentation
- Q&A
- Closing

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Presentation Outline

• Outline:
  • Molecular basis of aging
  • Calorie restriction and anti-aging: the evidence
    • Preclinical trials
    • Human observational
    • Human clinical trials
  • Concerns & counterpoints

• Objectives:
  Understand the biological basis of aging
  Describe the proposed mechanisms by which calorie restriction slows aging
What do I do?

Clinical-Translational Research
Intersection of multiple approaches:
• Cell Culture
• Clinical Metabolism
• Lifestyle Intervention

Private Practice
Cake Nutrition, LLC
• Metabolic Consultation
• Behavioral Counseling

Dietetic Leadership
Academy of Nutrition and Dietetics
• Volunteer opportunities
• Writing, reviewing, presenting
Longevity is dictated by the aging process

- Longevity = lifespan.
- Aging = decline in physiological function.
  - Affected by intrinsic (primary) and extrinsic (secondary) factors.
Longevity increasing ... until recently

- Sanitation
- Public Health
- Food Supply
- Malnutrition
- Healthcare

Largely extrinsic/secondary factors

Source: Riley (2005), Clio Infra (2015), and UN Population Division (2019)
Note: Shown is period life expectancy at birth, the average number of years a newborn would live if the pattern of mortality in the given year were to stay the same throughout its life.
The aging process is inevitable

- Decline in multiple physiological functions.
- Culminates in death of the organism.
- Humans: ↓fat-free mass, ↑weight & fat mass

- Primary aging – intrinsic factors; associated with:
  - Oxidative stress
  - Metabolic rate

- Secondary aging – extrinsic factors
  - Accelerates primary aging & mortality
Molecular basis of aging: “Seven Pillars”

Macromolecular Damage

Metabolism

Stem Cells and Regeneration

Epigenetics

Inflammation

Proteostasis

Adaptation to Stress

Kennedy Cell 2016
Endless Pursuit for a Fountain of Youth

Calorie Restriction
1. Dietary energy intake < requirements
2. Maintain optimal essential nutrient intake

Unique potential to slow aging!
Diving into the Evidence

- Pre-clinical evidence
- Human observational reports
- Clinical Trials
Pre-clinical: Drosophila

Graph showing the relationship between food level (proportion SY) and index of lifetime egg production (mean +/95% CI). The graph also shows the lifespan (median days from commencement of experimental treatment) as a function of food level.
Pre-clinical: Drosophila

Pre-clinical: Drosophila

Pre-clinical: Murine Models

• Classic trial 1935
• McCay, Crowell, and Maynard
• “The Effect of Retarded Growth upon the Length of Life Span and upon the Ultimate Body Size”

McCay 1935 J Nutr
McDonald 2010 J Nutr
Pre-clinical: Murine Models

- MANY different murine models
- 40% restriction in 41 genetic strains

Liao 2010 Aging Cell

 Raises concerns for translation to humans
Pre-clinical: Non-human Primates

- Genome shares 93% sequence identity with humans
- More similar to humans (decades of life, grey hair, muscle loss) than other models

Three overlapping studies
- U of Maryland
- U of Wisconsin
- National Institutes of Health
Pre-clinical: Non-human Primates

- University of Maryland rhesus monkey study
- 117 monkeys (Macaca mulatta)

Data collection started 1977

- Caloric restriction increases median age of survival ~7 years

Figure 1. Estimated survival curves comparing the dietary-restricted monkeys

Pre-clinical: Non-human Primates

- University of Wisconsin

- Most prominent effects
  1. Delays the onset of age-associated pathologies
  2. Promotes survival

Colman 2009 Science
Pre-clinical: Non-human Primates

- National Institutes of Health
- No significant effect on survival
- Why?
  - Variability in environment and/or unknown factors (study design, housing animals, diet composition)

Mattison 2012 Nature
Summary of the Evidence

Preclinical

• Calorie restriction is the only non-genetic method that extends lifespan in every species studied (50–300%)
  • Variability between and among species exist.
  • Translation to human remains in question.
Human Observational: Blue Zones

5 Areas with highest prevalence of centenarians

Joint venture to discover lifestyles for longevity:
- Dan Buettner
- National Geographic
- National Institute on Aging

Human Observational: Okinawans

- Small island of Japan
- Unique dietary habits
- Naturally restricted dietary intake to ~11% less than mainland

**Human Observational: Okinawans**

- Longer lifespan
- More centenarians
- Less age-related diseases
- Effects dissipated after Westernization
- Today, similar to other Westernized countries

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1 Average life span (50th percentile survival).
2 Maximum life span (99th percentile survival).
Human Observational: Biosphere II

- Biosphere-II experiment
- American Earth system science (closed ecosystem)
- Oracle, Arizona
- Studies to inform life in outer space
Biosphere II

- 8 volunteers, 2 years, 3.15 acre system
- Insufficient food production – unintentional calorie restriction
  - Low energy, but sufficient micronutrients
- Improved cardiovascular risk factors
- ↓ metabolic rate

Weyer 2000 Am J Clin Nutr
Human Observational: Calorie Restriction Society International

- Started by Roy Walford (Biosphere II volunteer)
- Free-living group
- Practice Caloric Restriction with Optimal Nutrition
  - “CRONies”
- Restrict energy intake ~1100-1950 kcals/day
  - Meet micronutrient needs
- BMI 19.6 ± 1.9
- Healthier cardiovascular markers vs controls

Fontana 2004 PNAS
Summary of the Evidence

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Human Observational

- Calorie restriction reduces age-related disease and mortality risk.
- Improves secondary aging.
- Impact on primary aging suggestive, but unclear.
Clinical Trials: Minnesota Starvation Experiment

Classic landmark trial by Ancel Keys
1944, University of Minnesota
*The Laboratory of Physiological Hygiene*

Motivation: post-war rehabilitation
→ instrumental in famine relief programs today

Goal: observe physical and mental effects of semi-starvation

Subjects: 36 conscientious objectors

Keys A 1950 University of Minnesota Press
Clinical Trials: Minnesota Starvation Experiment

Body Weight

C1  C12  S1  S24

Control  Semi-starvation  Restricted Refeeding  Ad libitum Refeeding

R1  R12  R20

Dulloo AG 2021 Obesity Reviews
Clinical Trials: Minnesota Starvation Experiment

Methods:
~60% of habitual dietary intake, foods mimic starvation conditions
e.g., bland, low variety, missing micronutrients
Walk 22 miles/week

Results:
~24% weight loss
Malnutrition with multiple nutrient deficiencies
First report of physical & psychological effects
Clinical Trials: Minnesota Starvation Experiment

Recall

Calorie Restriction

1. Dietary energy intake < requirements
2. Maintain essential nutrient intake
Clinical Trials: CALERIE

Comprehensive Assessment of the Long-term Effects of Reducing Intake of Energy

- 6 month calorie restriction
- 48 overweight men & women
- 25% restriction
  - 25% diet
  - 12.5% diet + 12.5% exercise
  - VLCD to 15% weight loss

Heilbronn 2006 JAMA
Clinical Trials: CALERIE

Slowed intrinsic factors to aging (primary aging)
↓ fasting insulin
↓ body temperature

Figure 6. Fasting Plasma Protein Carbonyls and DNA Damage Measured by the Comet Assay

DNA damage was significantly reduced from baseline in the calorie restriction, calorie restriction with exercise, and very low-calorie diet groups at month 6 (all P<.005).

Heilbronn 2006 JAMA
Clinical Trials: CALERIE II

- Larger, longer follow-up to CALERIE
- 2 years of calorie restriction (goal: 25% reduction from baseline)
- 220 adults 21-50 years old, without obesity
Clinical Trials: CALERIE II

Enrollment
- 238 Eligible

Allocation
- Randomized (N=220)
  - 18 Dropped During Baseline
    - Withdrew Consent (n=5)
    - Found ineligible (n=10)
      - Anemia (n=2)
      - Low BMD (n=8)
      - Other (n=3)

Follow-up
- 117 Completed Intervention
  - 26 Stopped Intervention:
    - 3 women became pregnant
    - 6 moved away from study site
    - 3 withdrawn for safety
    - 8 withdrew consent
    - 6 personal and other reasons
- 71 Completed Intervention
  - 4 Stopped Intervention:
    - 3 women became pregnant
    - 1 withdrew consent

Ravussin 2015 Journals of Gerontology
Clinical Trials: CALERIE II

- Primary outcomes
  - Resting metabolic rate
  - Core body temperature
  - No change
CALERIE II

- Other Cardiovascular outcomes
  - Significantly improved

- Secondary aging/extrinsic factors
CALERIE II

Significant loss of lean mass

Das 2017 Am J Clin Nutr
CALERIE II  Lean mass loss relatively proportional to overall mass loss

Das 2017 Am J Clin Nutr

All Subjects   Men   Women
Summary of the Evidence

Preclinical
• Calorie restriction is the only non-genetic method that extends lifespan in every species studied (50–300%).
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Human Observational
• Calorie restriction reduces age-related disease and mortality risk.
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Clinical Trials
• Prolonged calorie restriction is safe and tolerated well
  • Appears to improve some mechanisms of primary aging
  • Reduces biomarkers related to age-related disease and secondary aging
  • No incidence of eating disorder development
• Few clinical trials have been conducted

Williamson 2008 Health Psychol.
Concerns & Caveats

• Loss of bone mineral density
• Loss of muscle mass
• Sarcopenia definition only recently defined and ICD10 established

Severin 2018 Topics in Geriatric Rehabilitation
Concerns and Caveats: Protective effects of BMI

Lowest mortality risk: BMI 23-25 kg/m²
Concerns and Caveats: Protective effects of BMI

Right-shifted in Aging

Lowest mortality risk: BMI 27-28 kg/m²

Winter 2014 Am J Clin Nutr
Concerns and Caveats: Restriction
Forever or Bust?

~50% lost weight was ...

Maintained vs Regained

Marlatt 2017 Am J Clin Nutr
Overall State of the Evidence

Additional Limitations:
- Inherent issues to longevity research
- Variable effect on different factors of aging
- Few clinical trials
Take-home Message

- **Prolonged calorie restriction:**
  - Increases lifespan in preclinical models
  - Is viable in humans
  - Is the only approach evidenced (not proven) to slow primary aging
  - Consistently improves factors of secondary aging in humans
  - Has significant limitations and concerns
Deciphering a Clinical Application

- Flys, worms, mice = 50-300% increased lifespan
- Rhesus monkeys = 0-25% increased median survival
- Bluezones/Okinawa/CRONies = increased mean survival, reduced disease
- Minnesota Starvation Study = Critical concept
  - calorie restriction must come with optimal nutrition
- CALERIE I & II = Calorie restriction in healthy humans:
  1. is the only intervention that impacts facets of primary aging
  2. produces profound benefits on secondary aging
    - 10-15% caloric restriction w/ optimal nutrition
    - May be less useful to initiate as an older adult (65+)
Thank you!
Thank you for joining us today.

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