Nutrition and Fasting Mimicking Diets, Longevity and Rejuvenation

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Disclosure Statement of Financial Interest

I, Valter Longo, have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation, they are:

Affiliation/Financial Interest: Name of Organization (s):
Major Stock/Shareholder: L-Nutra

100% of these shares will be donated to charity
How much longer would we live if we cured cancer?

<table>
<thead>
<tr>
<th>Longevity Extension (yrs)</th>
<th>20 years?</th>
<th>25 years?</th>
<th>3 – 4 years</th>
</tr>
</thead>
</table>
How much longer would we live if we cured cancer, heart disease, stroke, and diabetes?

<table>
<thead>
<tr>
<th>Longevity Extension (yrs)</th>
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<tbody>
<tr>
<td>Cure cancer, heart disease, stroke, and diabetes</td>
</tr>
<tr>
<td>Delay aging half as effectively as we have done in mice</td>
</tr>
</tbody>
</table>
Juventology:

How Do We Stay Young?
World's 'Oldest Woman' Celebrates 115th Birthday in LA

*Never Drank or “Fooled Around”*

Gertrude Baines celebrating her birthday at the Western Convalescent Hospital in Los Angeles
Salvatore Caruso – 110 years old, Calabria Italy

“No wine, No tobacco, No Venus”
Jean Calment of France Lived Until 122 Years of Age

Smoked until 117 and believed red wine helped her get there
Emma Morano, 117 years old, Verbania, Italy, the oldest person in the world

Ate 3 eggs and meat almost every day
Treat Aging
Yeast, Flies, and Mice with Similar Genetic Mutations Live Longer and Healthier

Half of the long-lived growth hormone receptor and IGF-1 deficient mice never develop diseases vs. 10% for the normal mice

Growth Hormone Receptor and IGF-1 Deficient (GHRD) (Larons) Subjects

J. Guevara and The Little Women of Loja Ecuador

Ecuador, 2006
Humans With a Mutation in the Growth Hormone Receptor (GHRDs) are Protected From Diseases

Incidence of Cancer Deaths

Prevalence of Diabetes

- Cancer Deaths (%)
  - Relatives: 20%
  - GHRDs: 0%

- Prevalence (%)
  - Ecuador:
    - Obesity: 10%
    - Diabetes: 5%
  - GHRD:
    - Obesity: 20%
    - Diabetes: 10%
Humans With a Mutation in the Growth Hormone Receptor (GHRDs) are Protected From Diseases

Incidence of Cancer Deaths

Prevalence of Diabetes

- Ecuador
- GHRD

Priya Balasubramanian
The Longevity Diet
Calorie restricted monkeys have reduced mortality from major diseases but do not live much longer.

**Diabetes**
--60% of animals on normal diet
--Absent in CR monkeys.

**Tumors and cardiovascular diseases**
--Reduced by 50% in CR monkey
8 people lived inside Biosphere II, Arizona for 2 years

**Diet:** they consumed a plant based 30% calorie restricted diet

**Calorie Restriction**
- Reduces markers of:
  - Cancer
  - Heart Disease
  - Diabetes
  - Hypertension
Effects of calorie restriction on disease risk factors

BODY MASS INDEX

GLUCOSE

SYSTOLIC BLOOD PRESSURE

CHOLESTEROL

WALFORD et at.
Calorie restriction is extreme

Dr. Roy Walford (UCLA)

In Biosphere 2  
Calorie Restricted

After Biosphere 2  
Healthy Diet
Starved Organisms Live Longer

**Bacteria**

*Survival (%) vs. Hours*

**Baker’s Yeast**

*Survival (%) vs. Days*

**Worms**

*Fraction Surviving vs. Age (days)*

Images per Wikipedia public domain.
Periodic Fasting Mimicking Diet (FMD)

Developed a mouse diet (FMD) that is as effective as water only fasting in altering markers including IGF-1, IGFBP1, glucose and ketone bodies

FMD
• Low calorie,
• Low sugar,
• Low protein,
• High unsaturated fats
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.

White Blood Cells

Counts ($10^9$/L)

Young | Old | Old + FMD

Fasting Mimicking Diet cycles reduce and delay cancer

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

Only the combination of chemotherapy and fasting promotes cancer free survival in mice.

Lung cancer

Breast cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Lung Cancer % Cancer Free</th>
<th>Breast Cancer % Cancer Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chemo therapy</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Fasting</td>
<td>0</td>
<td>40</td>
</tr>
</tbody>
</table>

% cancer free
Only the combination of chemotherapy and fasting promotes cancer free survival in mice.

<table>
<thead>
<tr>
<th>Lung cancer</th>
<th>Breast cancer</th>
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<tbody>
<tr>
<td>% cancer free</td>
<td>% cancer free</td>
</tr>
<tr>
<td>No treatment</td>
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</tr>
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<td>Chemo therapy</td>
<td>Chemo therapy</td>
</tr>
<tr>
<td>Fasting</td>
<td>Fasting</td>
</tr>
<tr>
<td>Fasting + Chemo</td>
<td>Fasting + Chemo</td>
</tr>
</tbody>
</table>
Fasting/FMD-dependent Differential Stress Resistance (DSR) and Sensitization (DSS)

Nencioni A, Longo VD Nature Cancer Reviews 2018
Can the regenerative effect of fasting/FMD on the immune system enhance the T cell-mediated killing of cancer cells?
Tumor Infiltrating Lymphocytes are required for the effect of the fasting/FMD on cancer progression

FMD = Fasting-Mimicking Diet

Stefano Di biase, PhD

Di Biase et al Cancer Cell, 2016
Tumor Infiltrating Lymphocytes are required for the effect of the fasting/FMD on cancer progression

Cancer grows more rapidly in the absence of CD8 T Cells

Di Biase et al Cancer Cell, 2016
Mechanisms of Fasting/FMD-dependent Differential Stress Sensitization (DSS)

Nencioni A, Longo VD Nature Reviews Cancer 2018
Fasting and cancer

Clinical trials
Phase I Clinical trial (USC Norris Cancer Center): 72 hours of fasting is associated with reduced adverse effects in patients receiving gemcitabine/cisplatin, carboplatin/taxol

Collaboration with Tanya Dorff and David Quinn

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>24 hours # (%) N = 6</th>
<th>48 hours # (%) N = 7</th>
<th>72 hours # (%) N = 7</th>
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</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 or 2</td>
<td>6 (100%) 5 (83%)</td>
<td>6 (86%) 3 (43%)</td>
<td>3 (43%) 0</td>
</tr>
<tr>
<td>Grade 1 or 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 or 2</td>
<td>1 (17%) 4 (67%)</td>
<td>3 (43%) 1 (14%)</td>
<td>1 (14%) 2 (29%)</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 or 2</td>
<td>4 (67%) 0</td>
<td>1 (14%) 1 (14%)</td>
<td>1 (14%) 0</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
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<tr>
<td>Laboratory / Metabolic</td>
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<tr>
<td>Hypokalemia (low K)</td>
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<td></td>
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</tr>
<tr>
<td>Grade 1</td>
<td>1 (17%) 4 (67%)</td>
<td>2 (28%) 1 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1 and 2</td>
<td></td>
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<tr>
<td>Hyperglycemia</td>
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<tr>
<td>Elevated AST/ALT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>4 (67%) 0</td>
<td>0</td>
<td>3 (43%)</td>
</tr>
<tr>
<td>Neurologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>3 (50%) 1 (14%)</td>
<td>1 (14%)</td>
<td></td>
</tr>
</tbody>
</table>
The effects of short-term fasting on tolerance to (neo) adjuvant chemotherapy in HER2-negative breast cancer patients: a randomized pilot study

Stefanie de Groot, Maaike PG Vreeswijk, Marij JP Welters, Gido Gravesteijn, Jan JWA Boei, Anouk Jochems, Daniel Houtsma, Hein Putter, Jacobus JM van der Hoeven, Johan WR Nortier, Hanno Pijl, and Judith R Kroep
The effects of short-term fasting on quality of life and tolerance to chemotherapy in patients with breast and ovarian cancer: a randomized cross-over pilot study

Stephan P. Bauersfeld, Christian S. Kessler, Manfred Wischniewsky, Annette Jaensch, Nico Steckhan, Rainer Stange, Barbara Kunz, Barbara Brückner, Jalid Sehouli and Andreas Michelsen

Abstract

Background: This pilot trial aimed to study the feasibility and effects on quality of life (QOL) and well-being of short-term fasting (STF) during chemotherapy in patients with gynaecological cancer.

Methods: In an individually-randomized cross-over trial patients with gynaecological cancer, 4 to 6 planned chemotherapy cycles were included. Thirty-four patients were randomized to STF in the first half of chemotherapies followed by normocaloric diet (group A: n = 18) or vice versa (group B: n = 16). Fasting started 36 h before and ended 24 h after chemotherapy (60 h-fasting period). QOL was assessed by the FACT-G measurement system.

Results: The chemotherapy-induced reduction of QOL was less than the Minimally Important Difference (MID, FACT-G = 5) with STF but greater than the MID for non-fasted periods. The mean chemotherapy-induced deterioration of total FACT-Gen was 10.4 ± 5.3 for fasted and 27.0 ± 6.3 for non-fasted cycles in group A and 14.1 ± 5.6 for non-fasted and 11.0 ± 5.6 for fasted cycles in group B. There were no serious adverse effects.

Conclusion: STF during chemotherapy is well tolerated and appears to improve QOL and fatigue during chemotherapy. Larger studies should prove the effect of STF as an adjunct to chemotherapy.

Trial registration: This trial was registered at clinicaltrials.gov: NCT01954836

Keywords: Breast cancer, Chemotherapy, Fasting, Pilot study, Quality of life, Ovarian cancer
Chemotherapy-induced decrease of QOL with or without fasting/FMD

Fasting: C1 - C3 group B

Normal Diet: C4 – C6 group A
Targeting Cancer Metabolism: Dietary and Pharmacologic Interventions, Claudio Vernieri, Stefano Casola, Marco Foiani, Filippo Pietrantonio, Filippo de Braud and Valter Longo
How do a sperm cell and an egg from 40 year old parents generate a perfect zygote and baby?
How do a sperm cell and an oocyte from 40 year old parents generate a perfect zygote and baby?
Periodic Fasting Mimicking Diet (FMD) and Autoimmunity
Cycles of Fasting Mimicking Diet Reduce Multiple Sclerosis-like Symptoms in mice
(autoimmune Encephalomyelitis EAE model induced by myelin oligodendrocyte glycoprotein 35–55)

Inyoung Choi, PhD

Choi et al, Cell Reports, 2016
FMD Cycles Reduce Immune Cell Infiltration and Demyelination

Choi et al, Cell Reports, 2016
Summary (FMD and autoimmunity)
Pilot Clinical Data Indicates Improved Quality of Life after FMD in MS Patients

N= 45
Choi et al, Cell Reports, 2016

By Markus Bock and Andreas Michalsen, Charite’
Periodic Fasting Mimicking Diet (FMD) and Diabetes
FMD Reverses Hyperglycemia and Prevents Death in T2D model
(leptin receptor deficient db/db mice)

Chia Wei Cheng, PhD
Roberta Buono, PhD
Valentina Villani, PhD

Cheng et al, Cell 2017
FMD Cycles Reverses T1D in a streptozotocin (STZ) Model

Cheng et al, *Cell* 2017
FMD increases expression of Ngn3 and other genes expressed during embryonic development
Summary

Diabetes T1 and 2

- β-cell deficiency
- Low insulin secretion
- High blood glucose

Fasting mimicking diet (FMD)

PKA \downarrow mTOR

Human \uparrow Sox2 \uparrow Ngn3

Mouse \uparrow Sox17 \uparrow Ngn3

Activation of Ngn3+ progenitors

Generation of insulin-producing β cells

Normal

- β-cell regeneration
- Normal insulin secretion
- Normal blood glucose

Cheng et al, Cell 2017
HUMAN TRIAL: Fasting Mimicking Diet (FMD)

100 Participants randomized trial, 5 days a month for 3 months

V. Longo is the founder of L-Nutra. 100% of his shares will be donated to charitable organizations.
Fasting Mimicking Diet

Abdominal fat loss without loss in lean body mass

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Abdominal Fat</th>
<th>Waist Circumference</th>
<th>Lean Body Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>lbs</td>
<td>rel %</td>
<td>inches</td>
<td>rel %</td>
</tr>
<tr>
<td>170</td>
<td>10</td>
<td>38</td>
<td>68</td>
</tr>
<tr>
<td>167</td>
<td>9.5</td>
<td>37</td>
<td>66</td>
</tr>
<tr>
<td>164</td>
<td>9</td>
<td>36</td>
<td>65</td>
</tr>
<tr>
<td>161</td>
<td>9</td>
<td>35</td>
<td>64</td>
</tr>
</tbody>
</table>

Before | After | Before | After | Before | After | Before | After |

- Body Weight: From 170 lbs to 161 lbs
- Abdominal Fat: From 10 rel % to 9 rel %
- Waist Circumference: From 38 inches to 35 inches
- Lean Body Mass: From 68 rel % to 64 rel %
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

![Graph showing stem cells percentage under normal diet and FMD](image-url)
Rejuvenation from within

Periodic Fasting Mimicking Diet

Reduction in risk for age-related diseases:
- Diabetes
- Cancer
- CVD
- Alzheimer’s
Awakening the rejuvenation from within

Dr. Roy Walford – Biosphere 2

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