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L-Nutra Scientific Article

Cell Metabolism
Clinical and Translational Report

A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan

Sebastian Brandhorst,[1,15] In Young Choi,[1,15] Min Wei,[1] Chia Wei Cheng,[1] Sargis Sedrakyan,[2] Gerardo Navarrete,[1] Louis Dubeau,[3] Li Peng Yap,[4] Ryan Park,[4] Manlio Vinciguerra,[5] Stefano Di Biase,[1] Hamed Mirzaei,[1] Mario G. Mirisola,[6] Patra Childress,[7] Lingyun Ji,[8] Susan Groshen,[9] Fabio Penna,[3] Patrizio Odetti,[10] Laura Perin,[2] Peter S. Conti,[4] Yuji Ikeno,[11] Brian K. Kennedy,[12] Pinchas Cohen,[1] Todd E. Morgan,[1] Tanya B. Dorff,[13] and Valter D. Longo[1,14,*]

[1]Longevity Institute, School of Gerontology, and Department of Biological Sciences, University of Southern California, Los Angeles, CA 90089, USA
[2]GOFARR Laboratory, Children's Hospital Los Angeles, Division of Urology, Saban Research Institute, University of Southern California, Los Angeles, CA 90089, USA
[3]Department of Pathology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, USA
[4]Molecular Imaging Center, Department of Radiology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, USA
[5]Institute for Liver and Digestive Health, Division of Medicine, University College London, Royal Free Hospital, London NW3 2PF, UK
[6]Department of Pathobiology and Medical Biotechnology, University of Palermo, 90100 Palermo, Italy
[7]Global Medicine Program, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, USA
[8]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, USA
[9]Department of Clinical and Biological Sciences, University of Torino, 10100 Torino, Italy
[10]Department of Internal Medicine, University of Genova, 16146 Genova, Italy
[11]Department of Pathology, Barshop Institute, University of Texas Health Science Center, San Antonio, TX 78229, USA
[12]Buck Institute for Research on Aging, Novato, CA 94945, USA
[13]Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, USA
[14]IFOM, FIRC Institute of Molecular Oncology, 20139 Milano, Italy
[15]Co-first author
*Correspondence: vlongo@usc.edu
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SUMMARY

Prolonged fasting (PF) promotes stress resistance, but its effects on longevity are poorly understood. We show that alternating PF and nutrient-rich medium extended yeast lifespan independently of established pro-longevity genes. In mice, 4 days of a diet that mimics fasting (FMD), developed to minimize the burden of PF, decreased the size of multiple organs/systems, an effect followed upon re-feeding by an elevated number of progenitor and stem cells and regeneration. Bi-monthly FMD cycles started at middle age extended longevity, lowered visceral fat, reduced cancer incidence and skin lesions, rejuvenated the immune system, and retarded bone mineral density loss. In old mice, FMD cycles promoted hippocampal neurogenesis, lowered IGF-1 levels and PKA activity, elevated NeuroD1, and improved cognitive performance. In a pilot clinical trial, three FMD cycles decreased risk factors/biomarkers for aging, diabetes, cardiovascular disease, and cancer without major adverse effects, providing support for the use of FMDs to promote healthspan.

INTRODUCTION

Dietary composition and calorie level are key factors affecting aging and age-related diseases (Antosh et al., 2011; Blagosklonny et al., 2009; Fontana et al., 2010; Gems and Partridge, 2013; López-Otín et al., 2013; Tatar et al., 2003). Dietary restriction (DR) promotes metabolic and cellular changes that affect oxidative damage and inflammation, optimize energy metabolism, and enhance cellular protection (Haigis and Yankner, 2010; Johnson et al., 2000; Lee et al., 2012b; Longo and Finch, 2003; Mair and Dillin, 2008; Narasimhan et al., 2009; Smith et al., 2008). Fasting, the most extreme form of DR, which entails the abstinence from all food, but not water, can be applied in a chronic manner as intermittent fasting (IF) or periodically as cycles of prolonged fasting (PF) lasting 2 or more days (Longo and Mattson, 2014). In rodents, IF promotes protection against diabetes, cancer, heart disease, and neuro-degeneration (Longo and Mattson, 2014). In humans, IF and less-severe regimens (e.g., consumption of approximately 500 kcal/day for 2 days a week) have beneficial effects on insulin, glucose, C-reactive protein, and blood pressure (Harvie et al., 2011).

PF cycles lasting 2 or more days, but separated by at least a week of a normal diet, are emerging as a highly effective strategy to protect normal cells and organs from a variety of toxins and toxic conditions (Raffaghello et al., 2008; Verweij et al., 2011) while increasing the death of many cancer cell types (Lee et al., 2012a; Shi et al., 2012). PF causes a decrease in blood glucose,

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SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

METABOLIC DISEASE

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

Min Wei,[1]* Sebastian Brandhorst,[1]* Mahshid Shelehchi,[1] Hamed Mirzaei,[1] Chia Wei Cheng,[1] Julia Budniak,[1] Susan Groshen,[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. Longo[1,7]†

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.

INTRODUCTION

Metabolic syndrome is defined by co-occurrence of three of five of the following conditions: abdominal obesity, elevated fasting glucose, elevated blood pressure, high serum triglycerides, and low levels of high-density lipoprotein (HDL) cholesterol (*1*). Affecting 47 million Americans (*2*), it is associated with a major increase in the risk of cardiovascular disease (CVD) and all-cause mortality (*3*). Although prolonged fasting or very low calorie fasting-mimicking diets (FMDs) can ameliorate the incidence of diseases such as cancer and multiple sclerosis in mice (*4*–*6*), randomized trials to assess fasting's ability to reduce markers/risk factors for aging and major age-related diseases have not been carried out (*7*–*9*). Prolonged fasting, in which only water is consumed for 2 or more days, reduces pro-growth signaling and activates cellular protection mechanisms in organisms ranging from single-cell yeast to mammals (*10*). In mammals, this is achieved in part by temporarily reducing glucose and circulating insulin-like growth factor 1 (IGF-1), a hormone well studied for its role in metabolism, growth, and development, as well as for its association with aging and cancer (*11*–*16*). Severe growth hormone receptor and IGF-1 deficiencies are associated with a reduced risk of cancer, diabetes, and overall mortality in humans (*17*, *18*).

Mice fed periodically with the FMD show extended healthspan and multisystem regeneration, reduced inflammation and cancer incidence, and enhanced cognitive performance (*5*). Despite its potential for disease prevention and treatment, prolonged fasting is difficult to implement in human subjects and may exacerbate preexisting nutritional deficiencies, making it not feasible and/or safe for children, the elderly, frail individuals, and even most of the healthy adults. We have investigated whether a dietary intervention more practical and safer than fasting could affect markers or risk factors for aging and diseases. To this end, we developed an FMD based on a diet previously tested in animals and designed to achieve effects similar to those caused by fasting on IGF-1, insulin-like growth factor–binding protein 1 (IGFBP-1), glucose, and ketone bodies (*17*). To prevent nutrient deficiency, this FMD provided between 3000 and 4600 kJ per day, as well as high micronutrient nourishment, to each human subject (*5*). We also previously showed the safety and feasibility of this intervention in 19 study participants who consumed three monthly cycles of this FMD lasting 5 days each (*5*).

We now report the results of a randomized controlled trial of 100 subjects, 71 of whom completed three cycles of the FMD either in a randomized phase ($n = 39$) or after being crossed over from a control diet group to the FMD group ($n = 32$). We evaluated the effects of the FMD on risk factors and markers for aging, cancer, metabolic syndrome, and CVDs in generally healthy participants ranging from 20 to 70 years of age.

RESULTS

Baseline data for all subjects

From April 2013 to July 2015, 100 study participants were randomized and assigned to either arm 1 ($n = 48$) or arm 2 ($n = 52$). At enrollment, independent of whether they completed the trial or not, subjects in the two arms were comparable for age, sex, race, and body weight (Table 1). Hispanics (27%) were underrepresented in the study population in

[1]Longevity Institute, School of Gerontology, and Department of Biological Sciences, University of Southern California, Los Angeles, CA 90089, USA. [2]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA. [3]Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA. [4]Department of Internal Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA. [5]Department of Internal and Complementary Medicine, Charité University Medical Center, 10117 Berlin, Germany. [6]Department of Clinical Medicine, Sapienza University, 00185 Rome, Italy. [7]IFOM Institute of Molecular Oncology, Italian Foundation for Cancer Research Institute of Molecular Oncology, 20139 Milan, Italy.
*These authors contributed equally to this work.
†Corresponding author. Email: vlongo@usc.edu

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ORIGINAL ARTICLE

Fasting-Mimicking-Diet does not reduce skeletal muscle function in healthy young adults: a randomized control trial

Mauro Nardon[1] · Massimo Venturelli[1] · Federico Ruzzante[1] · Valter D. Longo[2,3] · Matteo Bertucco[1]

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Abstract

Purpose The aim of this study was to evaluate the short- and long-term effects of the Fasting-Mimicking-Diet (FMD) intervention on neuromuscular parameters of force production in healthy young men.

Methods Twenty-four physically active men completed the study. Participants were randomly assigned to Fasting-Mimicking (FMD) or Normal Diet (ND) and asked to follow three cycles of dietary intervention. Neuromuscular parameters of force production during maximal voluntary isometric contractions (MVCs) with the leg extensors muscles and anthropometrics were measured at baseline (T0), at the end of the first cycle (T1), and 7–10 days after the 3rd cycle of the nutritional intervention (T2). The study was registered on Clinicaltrials.gov (No. NCT04476615).

Results There was a significant decrease in body mass at T1 for FMD (− 2.6 kg, Δ from baseline, on average; $p<0.05$) but not in ND (− 0.1 kg;). Neuromuscular parameters of force production, muscle volume, and MVC torque did not change or differ between groups across visits. Results were similar even when parameters were normalized by muscle volume.

Conclusion The consumption of FMD in a group of young healthy male subjects showed to be feasible, and it did not affect neuromuscular parameters of force production. The results suggest that FMD could be safely adopted by strength athletes without detrimental effects on force and muscle volume. Further research in clinical population at risk of muscle mass loss, such as elderly and obese subjects with sarcopenia, is warranted.

Keywords Fasting · Fasting-Mimicking-Diet · Muscle force · Neuromuscular performance · The twitch interpolation technique

Abbreviations

ANOVA	Analysis of variance
BMI	Body Mass Index
CR	Caloric restriction
DR	Dietary restriction
EMG	Electromyography
FMD	Fasting-Mimicking-Diet
IPAQ	International physical activity questionnaire
MRFD	Maximal rate of force development
MRR	Maximal rate of relaxation
MVC	Maximal voluntary isometric contraction
ND	Normal diet
PNS	Peripheral nerve stimulation
Qtw_{pot}	Potentiated single twitch
SF-12	12-Item Short Form Health Survey
SI	Stimulation intensity
VA	Voluntary activation

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✉ Matteo Bertucco
matteo.bertucco@univr.it

[1] Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Via Felice Casorati 43, 37131 Verona, Italy

[2] Longevity Institute and Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089, USA

[3] IFOM, FIRC Institute of Molecular Oncology, 20139 Milan, Italy

Introduction

Fasting, the practice of total or partial abstention from food, is an ancient practice that is shared among different religions and dates back thousands of years (Sarri et al. 2005; Trepanowski and Bloomer 2010; Persynaki et al. 2017). Some fasting regimes require only a caloric restriction (CR) of the daily dietary intake, while frequency and composition

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Article

The Effects of a Fasting Mimicking Diet on Skin Hydration, Skin Texture, and Skin Assessment: A Randomized Controlled Trial

Jessica Maloh [1,*], Min Wei [2], William C. Hsu [2], Sara Caputo [2], Najiba Afzal [1,3] and Raja K. Sivamani [1,4,5,6]

[1] Integrative Skin Science and Research, Sacramento, CA 95815, USA
[2] L-Nutra, Inc., Plano, TX 75024, USA
[3] School of Medicine, University of California-Davis, Sacramento, CA 95817, USA
[4] Department of Dermatology, University of California-Davis, Sacramento, CA 95816, USA
[5] College of Medicine, California Northstate University, Elk Grove, CA 95757, USA
[6] Pacific Skin Institute, Sacramento, CA 95815, USA
* Correspondence: jessica@integrativeskinresearch.com

Abstract: Diet and nutrition have been shown to impact dermatological conditions. This has increased attention toward integrative and lifestyle medicine in the management of skin health. Emerging research around fasting diets, specifically the fasting-mimicking diet (FMD), has provided clinical evidence for chronic inflammatory, cardiometabolic, and autoimmune diseases. In this randomized controlled trial, we evaluated the effects of a five-day FMD protocol, administrated once a month for three months, on facial skin parameters, including skin hydration and skin roughness, in a group of 45 healthy women between the ages of 35 to 60 years old over the course of 71 days. The results of the study revealed that the three consecutive monthly cycles of FMD resulted in a significant percentage increase in skin hydration at day 11 ($p = 0.00013$) and at day 71 ($p = 0.02$) relative to baseline. The results also demonstrated maintenance of skin texture in the FMD group compared to an increase in skin roughness in the control group ($p = 0.032$). In addition to skin biophysical properties, self-reported data also demonstrated significant improvement in components of mental states such as happiness ($p = 0.003$) and confidence (0.039). Overall, these findings provide evidence for the potential use of FMD in improving skin health and related components of psychological well-being.

Keywords: fasting-mimicking diet; skin hydration; skin texture

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1. Introduction

The utilization of integrative medicine and lifestyle interventions in the management of various health concerns has gained significant interest in recent years. A lifetime prevalence of 35–69% for the use of complementary medicine was found in patients who seek dermatological treatments [1]. Among the various modalities of integrative medicine, diet and nutrition play a particularly important role. By addressing the underlying dietary and nutritional factors that may contribute to skin concerns, dietary interventions in dermatology may offer a unique inside-out approach to care [2].

The relationship between diet, weight, and dermatological disease has been demonstrated in the literature. For example, high-glycemic load diets are associated with hyperinsulinemia which, in turn, can contribute to acne through increases in inflammation and androgen-mediated increases in sebum production [3]. A randomized controlled trial in those with acne found that intervention with a low-glycemic load diet improved insulin sensitivity and reduced total inflammatory lesion counts compared to control [4]. Furthermore, psoriasis has been associated with increased adiposity, with excess adipose tissue that contributes to a pro-inflammatory state [5]. A study was conducted to investigate the role of weight reduction on psoriasis with the use of a low-calorie, protein-based diet [5].

Skin Health

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Article

Fasting-mimicking diet and hormone therapy induce breast cancer regression

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Irene Caffa[1,14], Vanessa Spagnolo[2,3,14], Claudio Vernieri[2,4], Francesca Valdemarin[1,2], Pamela Becherini[1,5], Min Wei[6], Sebastian Brandhorst[6], Chiara Zucal[7], Else Driehuis[8,9], Lorenzo Ferrando[1], Francesco Piacente[1,2], Alberto Tagliafico[10], Michele Cilli[1], Luca Mastracci[11], Valerio G. Vellone[2,11], Silvano Piazza[7], Anna Laura Cremonini[1,5], Raffaella Gradaschi[1], Carolina Mantero[1], Mario Passalacqua[12], Alberto Ballestrero[1,5], Gabriele Zoppoli[1,5], Michele Cea[1,5], Annalisa Arrighi[5], Patrizio Odetti[1,5], Fiammetta Monacelli[1,5], Giulia Salvadori[2,3], Salvatore Cortellino[3], Hans Clevers[8,9,13], Filippo De Braud[2,4], Samir G. Sukkar[1], Alessandro Provenzani[7], Valter D. Longo[2,6,15] ✉ & Alessio Nencioni[1,5,15] ✉

Approximately 75% of all breast cancers express the oestrogen and/or progesterone receptors. Endocrine therapy is usually effective in these hormone-receptor-positive tumours, but primary and acquired resistance limits its long-term benefit[1,2]. Here we show that in mouse models of hormone-receptor-positive breast cancer, periodic fasting or a fasting-mimicking diet[3–5] enhances the activity of the endocrine therapeutics tamoxifen and fulvestrant by lowering circulating IGF1, insulin and leptin and by inhibiting AKT–mTOR signalling via upregulation of EGR1 and PTEN. When fulvestrant is combined with palbociclib (a cyclin-dependent kinase 4/6 inhibitor), adding periodic cycles of a fasting-mimicking diet promotes long-lasting tumour regression and reverts acquired resistance to drug treatment. Moreover, both fasting and a fasting-mimicking diet prevent tamoxifen-induced endometrial hyperplasia. In patients with hormone-receptor-positive breast cancer receiving oestrogen therapy, cycles of a fasting-mimicking diet cause metabolic changes analogous to those observed in mice, including reduced levels of insulin, leptin and IGF1, with the last two remaining low for extended periods. In mice, these long-lasting effects are associated with long-term anti-cancer activity. These results support further clinical studies of a fasting-mimicking diet as an adjuvant to oestrogen therapy in hormone-receptor-positive breast cancer.

Growth factor signalling through the phosphoinositide 3-kinase (PI3K)–AKT–mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAP kinase) axes enhances oestrogen receptor activity and frequently underlies endocrine resistance in breast tumours[1,2,6]. Water-only fasting or plant-based diets that are simultaneously low in calories, sugar and protein and proportionally high in fat (fasting-mimicking diets (FMDs)) reduce circulating growth factors such as insulin and IGF1[2,6,7]. Therefore, we hypothesized that these dietary interventions could be used to enhance the activity of oestrogen therapy (ET) and delay endocrine resistance.

Low-serum, low-glucose cell culture conditions designed to mimic the effects of fasting or FMD (referred to as short-term starvation, STS) increased the anti-tumour activities of tamoxifen and fulvestrant in $HR^+/HER2^-$ breast cancer (BC) cell lines, and similar results were obtained in mouse xenografts of the same cell lines subjected to weekly cycles of fasting or FMD (Fig. 1a, Extended Data Figs. 1, 2a, b). STS also increased the anti-tumour activity of tamoxifen in tumour organoids from patients with HR^+ BC^8, and weekly FMD cycles prevented acquired resistance to tamoxifen in mice (Extended Data Fig. 2c, d). Enhancement of ET activity through STS was dependent on the reduction in serum, but not glucose, as adding back glucose to the growth medium did not affect the observed potentiation (Extended Data Fig. 3a).

In mice, besides increasing β-hydroxybutyrate levels (Extended Data Fig. 3b) and lowering blood glucose (from 6.3 ± 0.6 mmol l^{-1} to 4.1 ± 0.3 mmol l^{-1} and 4.0 ± 0.9 mmol l^{-1}, respectively; $n = 4$), fasting or FMD modified the levels of circulating growth factors and adipokines

[1]IRCCS Ospedale Policlinico San Martino, Genoa, Italy. [2]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy. [3]IFOM, FIRC Institute of Molecular Oncology, Milan, Italy. [4]Medical Oncology and Hematology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy. [5]Department of Internal Medicine and Medical Specialties, University of Genoa, Genoa, Italy. [6]Longevity Institute, Leonard Davis School of Gerontology and Department of Biological Sciences, University of Southern California, Los Angeles, CA, USA. [7]Department of Cellular, Computational, and Integrative Biology (CIBIO), University of Trento, Trento, Italy. [8]Oncode Institute and Hubrecht Institute, Royal Netherlands Academy of Arts and Sciences, Utrecht, The Netherlands. [9]University Medical Center Utrecht, Utrecht, The Netherlands. [10]Department of Health Sciences, University of Genoa, Genoa, Italy. [11]Department of Integrated Surgical and Diagnostic Sciences, University of Genoa, Genoa, Italy. [12]Department of Experimental Medicine, University of Genoa, Genoa, Italy. [13]Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands. [14]These authors contributed equally: Irene Caffa, Vanessa Spagnolo. [15]These authors jointly supervised this work: Valter D. Longo, Alessio Nencioni. ✉e-mail: vlongo@usc.edu; alessio.nencioni@unige.it

Cancer

Caffa I, Spagnolo V, Vernieri C, Valdemarin F, Becherini P, Wei M, Brandhorst S, Zucal C, Driehuis E, Ferrando L, Piacente F, Tagliafico A, Cilli M, Mastracci L, Vellone VG, Piazza S, Cremonini AL, Gradaschi R, Mantero C, Passalacqua M, Ballestrero A, Zoppoli G, Cea M, Arrighi A, Odetti P, Monacelli F, Salvadori G, Cortellino S, Clevers H, De Braud F, Sukkar SG, Provenzani A, Longo VD, Nencioni A. Fasting-mimicking diet and hormone therapy induce breast cancer regression. Nature. 2020;583(7817):620-4. doi: 10.1038/s41586-020-2502-7. PubMed PMID: 32669709; PMCID: PMC7881940.
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ARTICLE

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Synergistic effect of fasting-mimicking diet and vitamin C against *KRAS* mutated cancers

Maira Di Tano[1,2], Franca Raucci[2], Claudio Vernieri[2,3], Irene Caffa[4,5], Roberta Buono[6,8], Maura Fanti[6], Sebastian Brandhorst[6], Giuseppe Curigliano[1,7], Alessio Nencioni[4,5], Filippo de Braud[1,3] & Valter D. Longo[2,6]✉

Fasting-mimicking diets delay tumor progression and sensitize a wide range of tumors to chemotherapy, but their therapeutic potential in combination with non-cytotoxic compounds is poorly understood. Here we show that vitamin C anticancer activity is limited by the up-regulation of the stress-inducible protein heme-oxygenase-1. The fasting-mimicking diet selectivity reverses vitamin C-induced up-regulation of heme-oxygenase-1 and ferritin in *KRAS*-mutant cancer cells, consequently increasing reactive iron, oxygen species, and cell death; an effect further potentiated by chemotherapy. In support of a potential role of ferritin in colorectal cancer progression, an analysis of The Cancer Genome Atlas Database indicates that *KRAS* mutated colorectal cancer patients with low intratumor ferritin mRNA levels display longer 3- and 5-year overall survival. Collectively, our data indicate that the combination of a fasting-mimicking diet and vitamin C represents a promising low toxicity intervention to be tested in randomized clinical trials against colorectal cancer and possibly other *KRAS* mutated tumors.

[1]University of Milan, Department of Oncology and Hemato-Oncology, Milan, Italy. [2] IFOM, FIRC Institute of Molecular Oncology, Milan, Italy. [3] Medical Oncology Department, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy. [4] Department of Internal Medicine, University of Genoa, Genoa, Italy. [5] IRCCS Ospedale Policlinico San Martino, Genoa, Italy. [6] Longevity Institute, Leonard Davis School of Gerontology and Department of Biological Sciences, University of Southern California, Los Angeles, CA, USA. [7] Division of Early Drug Development, European Institute of Oncology, IRCCS, Milan, Italy. [8] Present address: Department of Molecular Biology and Biochemistry, University of California, Irvine, CA, USA. ✉email: valter.longo@ifom.eu

Cancer

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Fasting mimicking diet as an adjunct to neoadjuvant chemotherapy for breast cancer in the multicentre randomized phase 2 DIRECT trial

Stefanie de Groot[1], Rieneke T. Lugtenberg[1], Danielle Cohen[2], Marij J. P. Welters[1], Ilina Ehsan[1], Maaike P. G. Vreeswijk[3], Vincent T. H. B. M. Smit[2], Hiltje de Graaf[4], Joan B. Heijns[5], Johanneke E. A. Portielje[1,6], Agnes J. van de Wouw[7], Alex L. T. Imholz[8], Lonneke W. Kessels[8], Suzan Vrijaldenhoven[9], Arnold Baars[10], Elma Meershoek-Klein Kranenbarg[11], Marjolijn Duijm-de Carpentier[11], Hein Putter[12], Jacobus J. M. van der Hoeven[1], Johan W. R. Nortier[1], Valter D. Longo[13,14], Hanno Pijl[15], Judith R. Kroep[1✉] & Dutch Breast Cancer Research Group (BOOG)[16,*]

Short-term fasting protects tumor-bearing mice against the toxic effects of chemotherapy while enhancing therapeutic efficacy. We randomized 131 patients with HER2-negative stage II/III breast cancer, without diabetes and a BMI over 18 kg m^{-2}, to receive either a fasting mimicking diet (FMD) or their regular diet for 3 days prior to and during neoadjuvant chemotherapy. Here we show that there was no difference in toxicity between both groups, despite the fact that dexamethasone was omitted in the FMD group. A radiologically complete or partial response occurs more often in patients using the FMD (OR 3.168, $P = 0.039$). Moreover, per-protocol analysis reveals that the Miller&Payne 4/5 pathological response, indicating 90-100% tumor-cell loss, is more likely to occur in patients using the FMD (OR 4.109, $P = 0.016$). Also, the FMD significantly curtails chemotherapy-induced DNA damage in T-lymphocytes. These positive findings encourage further exploration of the benefits of fasting/FMD in cancer therapy. Trial number: NCT02126449.

[1]Department of Medical Oncology, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands. [2]Department of Pathology, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands. [3]Department of Human Genetics, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands. [4]Department of Medical Oncology, Medical center Leeuwarden, P.O. Box 888, 8901 NR Leeuwarden, The Netherlands. [5]Department of Medical Oncology, Amphia, P.O. Box 90157, 4800 RL Breda, The Netherlands. [6]Department of Medical Oncology, Haga hospital, P.O. Box 40551, 2504 LN Den Haag, The Netherlands. [7]Department of Medical Oncology, Viecuri, 5912BL Venlo, The Netherlands. [8]Department of Medical Oncology, Deventer hospital, P.O. Box 5001, 7416 SE Deventer, The Netherlands. [9]Department of Medical Oncology, Noordwest hospital group, location Alkmaar, P.O. Box 501, 1815 JD Alkmaar, The Netherlands. [10]Department of Medical Oncology, Hospital Gelderse vallei, 6710 HN Ede, The Netherlands. [11]Department of Surgery, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands. [12]Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, P.O. Box 9600, 2300RC Leiden, The Netherlands. [13]Longevity Institute, School of Gerontology, and Department of Biological Sciences, University of Southern California, Los Angeles, CA 90089, USA. [14]IFOM FIRC Institute of Molecular Oncology, Via Adamello 16, Milan, Italy. [15]Department of Endocrinology, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands. [16]BOOG Study Center, P.O. Box 9236, 1006 AE Amsterdam, The Netherlands. *A list of authors and their affiliations appears at the end of the paper. ✉email: j.r.kroep@lumc.nl

Cancer

de Groot S, Lugtenberg RT, Cohen D, Welters MJP, Ehsan I, Vreeswijk MPG, Smit V, de Graaf H, Heijns JB, Portielje JEA, van de Wouw AJ, Imholz ALT, Kessels LW, Vrijaldenhoven S, Baars A, Kranenbarg EM, Carpentier MD, Putter H, van der Hoeven JJM, Nortier JWR, Longo VD, Pijl H, Kroep JR, Dutch Breast Cancer Research G. Fasting mimicking diet as an adjunct to neoadjuvant chemotherapy for breast cancer in the multicentre randomized phase 2 DIRECT trial. Nature communications. 2020;11(1):3083. doi: 10.1038/s41467-020-16138-3. PubMed PMID: 32576828; PMCID: PMC7311547.
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CLINICAL TRIAL

Quality of life and illness perceptions in patients with breast cancer using a fasting mimicking diet as an adjunct to neoadjuvant chemotherapy in the phase 2 DIRECT (BOOG 2013–14) trial

Rieneke T. Lugtenberg[1] · Stefanie de Groot[1] · Ad A. Kaptein[2] · Maarten J. Fischer[2] · Elma Meershoek-Klein Kranenbarg[3] · Marjolijn Duijm-de Carpentier[3] · Danielle Cohen[4] · Hiltje de Graaf[5] · Joan B. Heijns[6] · Johanneke E. A. Portielje[1,7] · Agnes J. van de Wouw[8] · Alex L. T. Imholz[9] · Lonneke W. Kessels[9] · Suzan Vrijaldenhoven[10] · Arnold Baars[11] · Marta Fiocco[12] · Jacobus J. M. van der Hoeven[1] · Hans Gelderblom[1] · Valter D. Longo[13,14] · Hanno Pijl[15] · Judith R. Kroep[1] · on behalf of the Dutch Breast Cancer Research Group (BOOG)[16]

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Abstract

Purpose In the phase II DIRECT study a fasting mimicking diet (FMD) improved the clinical response to neoadjuvant chemotherapy as compared to a regular diet. Quality of Life (QoL) and illness perceptions regarding the possible side effects of chemotherapy and the FMD were secondary outcomes of the trial.

Methods 131 patients with HER2-negative stage II/III breast cancer were recruited, of whom 129 were randomly assigned (1:1) to receive either a fasting mimicking diet (FMD) or their regular diet for 3 days prior to and the day of neoadjuvant chemotherapy. The European Organisation for Research and Treatment of Cancer (EORTC) questionnaires EORTC-QLQ-C30 and EORTC-QLQ-BR23; the Brief Illness Perception Questionnaire (BIPQ) and the Distress Thermometer were used to assess these outcomes at baseline, halfway chemotherapy, before the last cycle of chemotherapy and 6 months after surgery.

Results Overall QoL and distress scores declined during treatment in both arms and returned to baseline values 6 months after surgery. However, patients' perceptions differed slightly over time. In particular, patients receiving the FMD were less concerned and had better understanding of the possible adverse effects of their treatment in comparison with patients on a regular diet. Per-protocol analyses yielded better emotional, physical, role, cognitive and social functioning scores as well as lower fatigue, nausea and insomnia symptom scores for patients adherent to the FMD in comparison with non-adherent patients and patients on their regular diet.

Conclusions FMD as an adjunct to neoadjuvant chemotherapy appears to improve certain QoL and illness perception domains in patients with HER2-negative breast cancer.

Trialregister
ClinicalTrials.gov Identifier: NCT02126449.

Keywords Quality of life · Illness perceptions · Breast cancer · Chemotherapy · Short-term fasting · Fasting mimicking diet · Distress thermometer

Rieneke T. Lugtenberg and Stefanie de Groot have contributed equallyto this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10549-020-05991-x) contains supplementary material, which is available to authorized users.

✉ Judith R. Kroep
j.r.kroep@lumc.nl

Extended author information available on the last page of the article

Introduction

Short-term fasting (STF) during cancer treatment has attracted increasing attention since the first report of benefits in mice in 2008 [1]. Indeed, in rodents, fasting limits tumor proliferation and enhances the sensitivity of tumor cells to cancer therapies, while simultaneously protecting healthy cells against its toxic effects [2–4]. These experimental benefits triggered a number of small clinical trials exploring

Cancer

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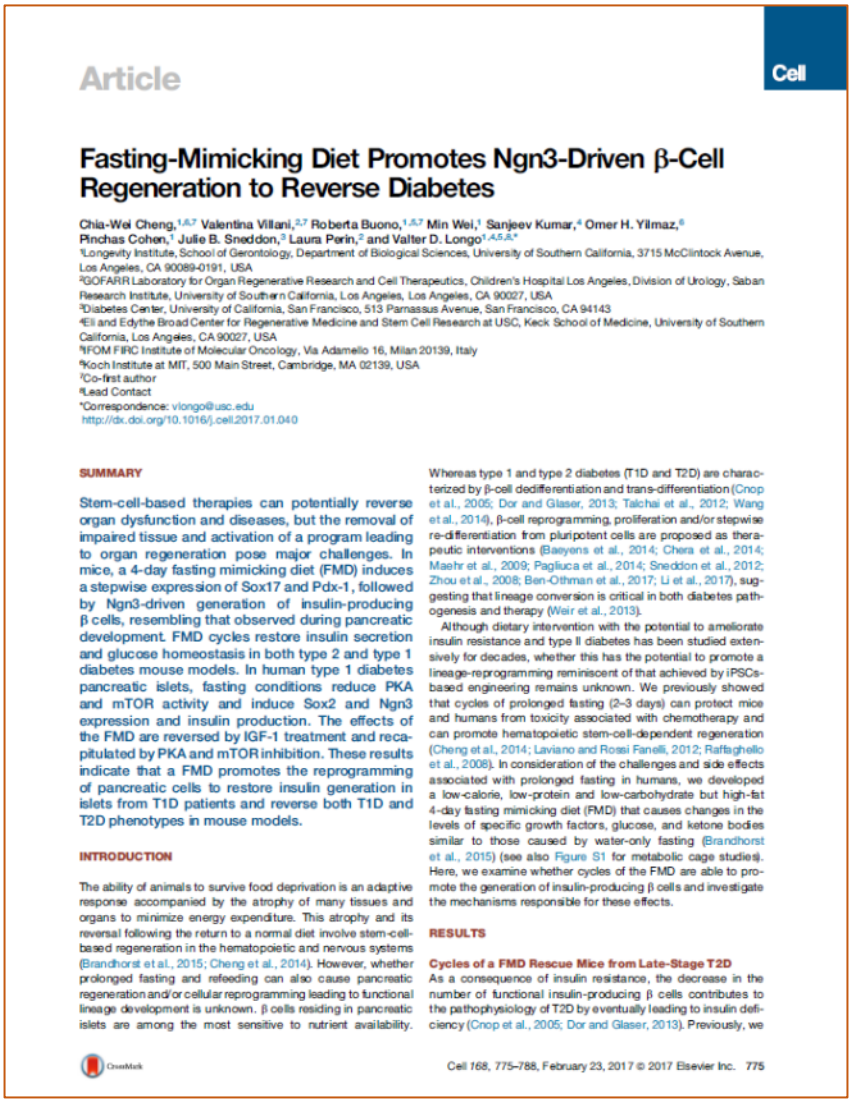

Article

Cell

Fasting-Mimicking Diet Promotes Ngn3-Driven β-Cell Regeneration to Reverse Diabetes

Chia-Wei Cheng,[1,6,7] Valentina Villani,[2,7] Roberta Buono,[1,6,7] Min Wei,[1] Sanjeev Kumar,[4] Omer H. Yilmaz,[5] Pinchas Cohen,[1] Julie B. Sneddon,[3] Laura Perin,[2] and Valter D. Longo[1,4,5,8,*]

[1]Longevity Institute, School of Gerontology, Department of Biological Sciences, University of Southern California, 3715 McClintock Avenue, Los Angeles, CA 90089-0191, USA

[2]IGOFARR Laboratory for Organ Regenerative Research and Cell Therapeutics, Children's Hospital Los Angeles, Division of Urology, Saban Research Institute, University of Southern California, Los Angeles, Los Angeles, CA 90027, USA

[3]Diabetes Center, University of California, San Francisco, 513 Parnassus Avenue, San Francisco, CA 94143

[4]Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC, Keck School of Medicine, University of Southern California, Los Angeles, CA 90027, USA

[5]IFOM FIRC Institute of Molecular Oncology, Via Adamello 16, Milan 20139, Italy

[6]Koch Institute at MIT, 500 Main Street, Cambridge, MA 02139, USA

[7]Co-first author

[8]Lead Contact

*Correspondence: vlongo@usc.edu

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SUMMARY

Stem-cell-based therapies can potentially reverse organ dysfunction and diseases, but the removal of impaired tissue and activation of a program leading to organ regeneration pose major challenges. In mice, a 4-day fasting mimicking diet (FMD) induces a stepwise expression of Sox17 and Pdx-1, followed by Ngn3-driven generation of insulin-producing β cells, resembling that observed during pancreatic development. FMD cycles restore insulin secretion and glucose homeostasis in both type 2 and type 1 diabetes mouse models. In human type 1 diabetes pancreatic islets, fasting conditions reduce PKA and mTOR activity and induce Sox2 and Ngn3 expression and insulin production. The effects of the FMD are reversed by IGF-1 treatment and recapitulated by PKA and mTOR inhibition. These results indicate that a FMD promotes the reprogramming of pancreatic cells to restore insulin generation in islets from T1D patients and reverse both T1D and T2D phenotypes in mouse models.

INTRODUCTION

The ability of animals to survive food deprivation is an adaptive response accompanied by the atrophy of many tissues and organs to minimize energy expenditure. This atrophy and its reversal following the return to a normal diet involve stem-cell-based regeneration in the hematopoietic and nervous systems (Brandhorst et al., 2015; Cheng et al., 2014). However, whether prolonged fasting and refeeding can also cause pancreatic regeneration and/or cellular reprogramming leading to functional lineage development is unknown. β cells residing in pancreatic islets are among the most sensitive to nutrient availability. Whereas type 1 and type 2 diabetes (T1D and T2D) are characterized by β-cell dedifferentiation and trans-differentiation (Cnop et al., 2005; Dor and Glaser, 2013; Talchai et al., 2012; Wang et al., 2014), β-cell reprogramming, proliferation and/or stepwise re-differentiation from pluripotent cells are proposed as therapeutic interventions (Baeyens et al., 2014; Chera et al., 2014; Maehr et al., 2009; Pagliuca et al., 2014; Sneddon et al., 2012; Zhou et al., 2008; Ben-Othman et al., 2017; Li et al., 2017), suggesting that lineage conversion is critical in both diabetes pathogenesis and therapy (Weir et al., 2013).

Although dietary intervention with the potential to ameliorate insulin resistance and type II diabetes has been studied extensively for decades, whether this has the potential to promote a lineage-reprogramming reminiscent of that achieved by iPSCs-based engineering remains unknown. We previously showed that cycles of prolonged fasting (2–3 days) can protect mice and humans from toxicity associated with chemotherapy and can promote hematopoietic stem-cell-dependent regeneration (Cheng et al., 2014; Laviano and Rossi Fanelli, 2012; Raffaghello et al., 2008). In consideration of the challenges and side effects associated with prolonged fasting in humans, we developed a low-calorie, low-protein and low-carbohydrate but high-fat 4-day fasting mimicking diet (FMD) that causes changes in the levels of specific growth factors, glucose, and ketone bodies similar to those caused by water-only fasting (Brandhorst et al., 2015) (see also Figure S1 for metabolic cage studies). Here, we examine whether cycles of the FMD are able to promote the generation of insulin-producing β cells and investigate the mechanisms responsible for these effects.

RESULTS

Cycles of a FMD Rescue Mice from Late-Stage T2D

As a consequence of insulin resistance, the decrease in the number of functional insulin-producing β cells contributes to the pathophysiology of T2D by eventually leading to insulin deficiency (Cnop et al., 2005; Dor and Glaser, 2013). Previously, we

Diabetes

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Clinical Research Article

Six-Month Periodic Fasting in Patients With Type 2 Diabetes and Diabetic Nephropathy: A Proof-of-Concept Study

Alba Sulaj,[1,2] Stefan Kopf,[1,2] Ekaterina von Rauchhaupt,[1,2] Elisabeth Kliemank,[1,2] Maik Brune,[1,3] Zoltan Kender,[1,2] Hannelore Bartl,[1] Fabiola Garcia Cortizo,[4] Katarina Klepac,[5] Zhe Han,[1] Varun Kumar,[1] Valter Longo,[6,7] Aurelio Teleman,[4], Jürgen G. Okun,[8] Jakob Morgenstern,[1,2] Thomas Fleming,[1,2] Julia Szendroedi,[1,2,3] Stephan Herzig,[2,5,9,10] and Peter P. Nawroth[1,2,3]

[1]Department of Endocrinology, Diabetology, Metabolism and Clinical Chemistry (Internal Medicine 1), Heidelberg University Hospital, Heidelberg, Germany
[2]German Center of Diabetes Research (DZD), Neuherberg, Germany
[3]Joint Heidelberg-IDC Translational Diabetes Program, Helmholtz Center Munich, Neuherberg, Germany
[4]German Cancer Research Center (DKFZ), Division of Signal Transduction in Cancer and Metabolism, Heidelberg, Germany
[5]Institute for Diabetes and Cancer, Helmholtz Center Munich, Neuherberg, Germany
[6]Longevity Institute, School of Gerontology, and Department of Biological Sciences, University of Southern California, Los Angeles, CA, USA
[7]FIRC Institute of Molecular Oncology, Italian Foundation for Cancer Research Institute of Molecular Oncology, Milan, Italy
[8]Department of General Pediatrics, Division of Neuropediatrics and Metabolic Medicine, Centre for Pediatric and Adolescent Medicine, University Hospital Heidelberg, Heidelberg, Germany
[9]Joint Heidelberg-IDC Translational Diabetes Program, Internal Medicine 1, Heidelberg University Hospital, Heidelberg, Germany; and
[10]Chair Molecular Metabolic Control, Technical University Munich, Munich, Germany

Correspondence: Alba Sulaj, MD, Clinic of Endocrinology, Diabetology, Metabolism and Clinical Chemistry, Im Neuenheimer Feld 410, 69120, Heidelberg, Germany. Email: Alba.Sulaj@med.uni-heidelberg.de.

Abstract

Context: Novel fasting interventions have gained scientific and public attention. Periodic fasting has emerged as a dietary modification promoting beneficial effects on metabolic syndrome.

Objective: Assess whether periodic fasting reduces albuminuria and activates nephropathy-driven pathways.

Design/Participants: Proof-of-concept study where individuals with type 2 diabetes (n = 40) and increased albumin-to-creatinine ratio (ACR) were randomly assigned to receive a monthly fasting-mimicking diet (FMD) or a Mediterranean diet for 6 months with 3-month follow-up.

Main Outcomes Measures: Change in ACR was assessed by analysis of covariance adjusted for age, sex, weight loss, and baseline value. Prespecified subgroup analysis for patients with micro- vs macroalbuminuria at baseline was performed. Change in homeostatic model assessment for insulin resistance (HOMA-IR), circulating markers of dicarbonyl detoxification (methylglyoxal-derived hydroimidazolone 1, glyoxalase-1, and hydroxyacetone), DNA-damage/repair (phosphorylated histone H2AX), lipid oxidation (acylcarnitines), and senescence (soluble urokinase plasminogen activator receptor) were assessed as exploratory endpoints.

Results: FMD was well tolerated with 71% to 95% of the participants reporting no adverse effects. After 6 months, change in ACR was comparable between study groups [110.3 (99.2, 121.5) mg/g; $P = 0.45$]. FMD led to a reduction of ACR in patients with microalbuminuria levels at baseline [−30.3 (−35.7, −24.9) mg/g; $P < 0.05$] but not in those with macroalbuminuria [434.0 (404.7, 463.4) mg/g; $P = 0.23$]. FMD reduced HOMA-IR [−3.8 (−5.6, −2.0); $P < 0.05$] and soluble urokinase plasminogen activator receptor [−156.6 (−172.9, −140.4) pg/mL; $P < 0.05$], while no change was observed in markers of dicarbonyl detoxification or DNA-damage/repair. Change in acylcarnitines was related to patient responsiveness to ACR improvement. At follow-up only HOMA-IR reduction [−1.9 (−3.7, −0.1), $P \leq 0.05$]) was sustained.

Conclusions: Improvement of microalbuminuria and of markers of insulin resistance, lipid oxidation, and senescence suggest the potential beneficial effects of periodic fasting in type 2 diabetes.

Key Words: diabetic nephropathy, periodic fasting, insulin resistance, dicarbonyl detoxification, lipid oxidation, senescence

Abbreviations: AC, acylcarnitines; ACR, albumin-to-creatinine ratio; C2, acetylcarnitine; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FMD, fasting-mimicking diet; Glo-1, glyoxalase-1; HOMA-IR, homeostatic model assessment of insulin resistance; M-Diet, Mediterranean diet; MDS, Mediterranean diet score; MG, methylglyoxal; MG-H1, methylglyoxal-derived hydroimidazolone 1; SGLT-2, sodium-glucose cotransporter-2; suPAR, soluble urokinase plasminogen activator receptor; pGlo-1, phosphorylated glyoxalase-1; WBC, white blood cells; γH2Ax, phosphorylated histone H2AX.

Diabetic nephropathy is the most common cause of end-stage renal disease, and therapeutic options for slowing its progression are limited to control of glycemia, lipidemia, and blood pressure (1). Current therapies, in particular, sodium-glucose cotransporter-2 (SGLT-2) inhibitors and angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers, exert nephroprotection to some degree (2, 3). However, the renal benefits attributed to SGLT-2

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Diabetes

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L-Nutra Scientific Article

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Cell Reports
Article

Fasting-Mimicking Diet Modulates Microbiota and Promotes Intestinal Regeneration to Reduce Inflammatory Bowel Disease Pathology

Priya Rangan,[1,6] Inyoung Choi,[1,6] Min Wei,[1] Gerardo Navarrete,[1] Esra Guen,[1] Sebastian Brandhorst,[1] Nobel Enyati,[2] Gab Pasia,[1] Daral Maesincee,[1] Vanessa Ocon,[1] Maya Abdulridha,[1] and Valter D. Longo[2,3,4,6,*]
[1]Longevity Institute, School of Gerontology, Department of Biological Sciences, University of Southern California, 3715 McClintock Avenue, Los Angeles, CA 90089-0191, USA
[2]USC Dornsife College of Letters, Arts & Sciences, Department of Biological Sciences, University of Southern California, 3551 Trousdale Pkwy, Los Angeles, CA 90089-0191, USA
[3]Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC, Keck School of Medicine, University of Southern California, 1425 San Pablo St, Los Angeles, CA 90033, USA
[4]IFOM FIRC Institute of Molecular Oncology, Via Adamello 16, Milano 20139, Italy
[6]These authors contributed equally
[6]Lead Contact
*Correspondence: vlongo@usc.edu
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SUMMARY

Dietary interventions are potentially effective therapies for inflammatory bowel diseases (IBDs). We tested the effect of 4-day fasting-mimicking diet (FMD) cycles on a chronic dextran sodium sulfate (DSS)-induced murine model resulting in symptoms and pathology associated with IBD. These FMD cycles reduced intestinal inflammation, increased stem cell number, stimulated protective gut microbiota, and reversed intestinal pathology caused by DSS, whereas water-only fasting increased regenerative and reduced inflammatory markers without reversing pathology. Transplants of *Lactobacillus* or fecal microbiota from DSS- and FMD-treated mice reversed DSS-induced colon shortening, reduced inflammation, and increased colonic stem cells. In a clinical trial, three FMD cycles reduced markers associated with systemic inflammation. The effect of FMD cycles on microbiota composition, immune cell profile, intestinal stem cell levels and the reversal of pathology associated with IBD in mice, and the anti-inflammatory effects demonstrated in a clinical trial show promise for FMD cycles to ameliorate IBD-associated inflammation in humans.

INTRODUCTION

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is associated with acute and chronic inflammation of the intestine. Risk factors include genetic predisposition and factors that alter gut microbiota, such as antibiotics (Manichanh et al., 2012). Although the effect of nutrition on IBD remains poorly understood, diets that cause pro-inflammatory changes in gut microbiota have consistently been associated with IBD pathogenesis (Kaplan and Ng, 2017).

Periodic fasting (PF) and fasting-mimicking diets (FMDs) have been effective in increasing healthy lifespan or as therapies in mouse models for a variety of diseases (Choi et al., 2017; Lee and Longo, 2016; Brandhorst et al., 2015). FMDs can reduce cancer incidence and aging-associated immunosuppression/immunosenescence, a process aided by hematopoietic stem-cell-based regeneration (Brandhorst et al., 2015; Cheng et al., 2014). Moreover, FMD cycles ameliorate or reverse disease progression in mouse models of multiple sclerosis (MS), and type I, and type II diabetes (Choi et al., 2016; Cheng et al., 2017). Recent studies also showed positive effects of a 24-hour fast on intestinal stem cell function in young and aged mice by a fatty acid oxidation pathway (Mihaylova et al., 2018).

Here, we report on the effect of cycles of a low-calorie and low-protein FMD in the treatment of a mouse model for IBD-related pathology and on its effects on inflammatory markers in humans. Our results indicate that FMD cycles cause a reduction in intestinal inflammation, increase intestinal stem cells (ISCs), and promote the expansion of beneficial gut microbiota, resulting in improvements in IBD-associated phenotypes.

RESULTS

FMD Cycles Ameliorate IBD-Associated Phenotypes

The dextran sodium sulfate (DSS)-induced colitis model is commonly used to study IBD in mice because DSS is a sulfated polysaccharide especially toxic to the colonic epithelium (Dupaul-Chicoine J. et al., 2010; Koblansky et al., 2016). The acute DSS model is implemented over 1–2 weeks and is used to achieve short-term alterations in the intestinal barrier, whereas the chronic DSS mouse model is implemented over a period of 2–4 months to cause long-term effects on intestinal immunity and damage, serving as an effective model for chronic colitis (Wirtz et al., 2017). Because genetic factors for IBD are currently

Inflammatory Bowel Diseases

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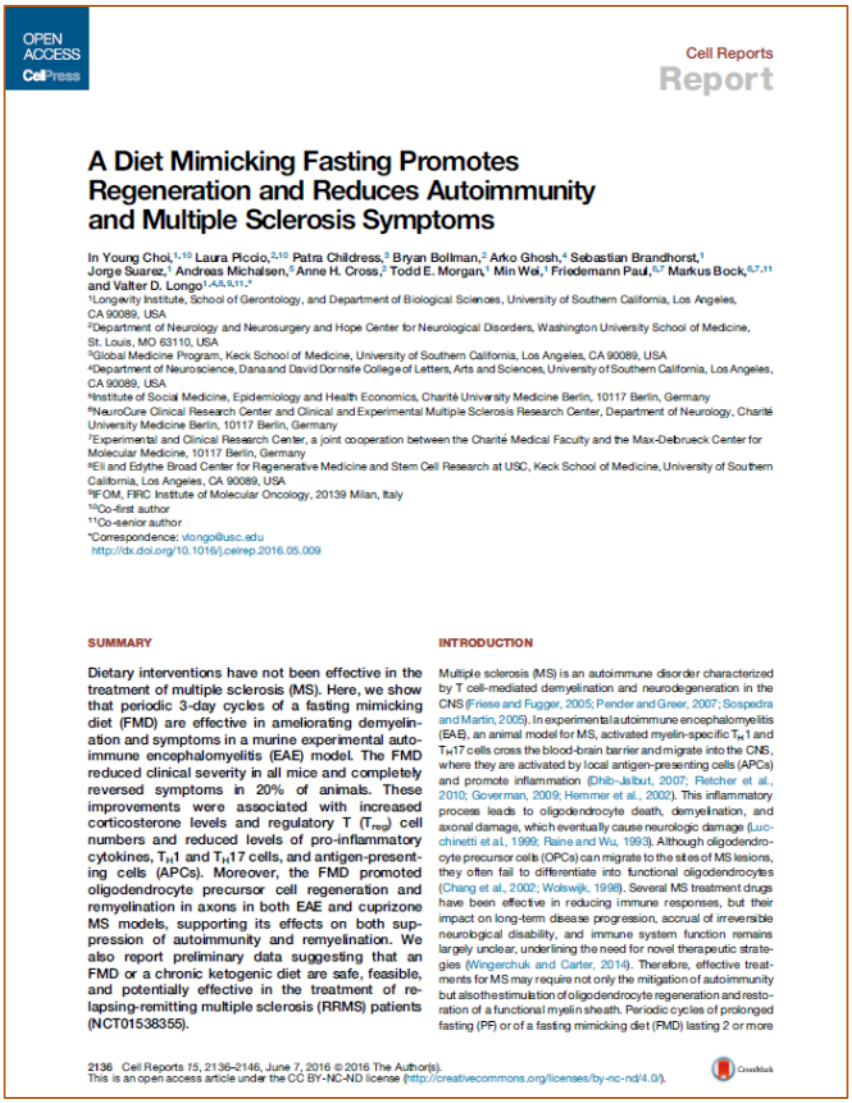
Rangan, 2019



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Cell Reports
Report

A Diet Mimicking Fasting Promotes Regeneration and Reduces Autoimmunity and Multiple Sclerosis Symptoms

In Young Choi,[1,10] Laura Piccio,[2,10] Patra Childress,[3] Bryan Bollman,[2] Arko Ghosh,[4] Sebastian Brandhorst,[1] Jorge Suarez,[1] Andreas Michalsen,[5] Anne H. Cross,[2] Todd E. Morgan,[1] Min Wei,[1] Friedemann Paul,[6,7] Markus Bock,[6,7,11] and Valter D. Longo[1,4,8,9,11,*]

[1]Longevity Institute, School of Gerontology, and Department of Biological Sciences, University of Southern California, Los Angeles, CA 90089, USA
[2]Department of Neurology and Neurosurgery and Hope Center for Neurological Disorders, Washington University School of Medicine, St. Louis, MO 63110, USA
[3]Global Medicine Program, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, USA
[4]Department of Neuroscience, Dana and David Dornsife College of Letters, Arts and Sciences, University of Southern California, Los Angeles, CA 90089, USA
[5]Institute of Social Medicine, Epidemiology and Health Economics, Charité University Medicine Berlin, 10117 Berlin, Germany
[6]NeuroCure Clinical Research Center and Clinical and Experimental Multiple Sclerosis Research Center, Department of Neurology, Charité University Medicine Berlin, 10117 Berlin, Germany
[7]Experimental and Clinical Research Center, a joint cooperation between the Charité Medical Faculty and the Max-Delbrueck Center for Molecular Medicine, 10117 Berlin, Germany
[8]Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, USA
[9]IFOM, FIRC Institute of Molecular Oncology, 20139 Milan, Italy
[10]Co-first author
[11]Co-senior author
*Correspondence: vlongo@usc.edu
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SUMMARY

Dietary interventions have not been effective in the treatment of multiple sclerosis (MS). Here, we show that periodic 3-day cycles of a fasting mimicking diet (FMD) are effective in ameliorating demyelination and symptoms in a murine experimental autoimmune encephalomyelitis (EAE) model. The FMD reduced clinical severity in all mice and completely reversed symptoms in 20% of animals. These improvements were associated with increased corticosterone levels and regulatory T (T_{reg}) cell numbers and reduced levels of pro-inflammatory cytokines, T_H1 and T_H17 cells, and antigen-presenting cells (APCs). Moreover, the FMD promoted oligodendrocyte precursor cell regeneration and remyelination in axons in both EAE and cuprizone MS models, supporting its effects on both suppression of autoimmunity and remyelination. We also report preliminary data suggesting that an FMD or a chronic ketogenic diet are safe, feasible, and potentially effective in the treatment of relapsing-remitting multiple sclerosis (RRMS) patients (NCT01538355).

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disorder characterized by T cell-mediated demyelination and neurodegeneration in the CNS (Friese and Fugger, 2005; Pender and Greer, 2007; Sospedra and Martin, 2005). In experimental autoimmune encephalomyelitis (EAE), an animal model for MS, activated myelin-specific T_H1 and T_H17 cells cross the blood-brain barrier and migrate into the CNS, where they are activated by local antigen-presenting cells (APCs) and promote inflammation (Dhib-Jalbut, 2007; Fletcher et al., 2010; Goverman, 2009; Hemmer et al., 2002). This inflammatory process leads to oligodendrocyte death, demyelination, and axonal damage, which eventually cause neurologic damage (Lucchinetti et al., 1999; Raine and Wu, 1993). Although oligodendrocyte precursor cells (OPCs) can migrate to the sites of MS lesions, they often fail to differentiate into functional oligodendrocytes (Chang et al., 2002; Wolswijk, 1998). Several MS treatment drugs have been effective in reducing immune responses, but their impact on long-term disease progression, accrual of irreversible neurological disability, and immune system function remains largely unclear, underlining the need for novel therapeutic strategies (Wingerchuk and Carter, 2014). Therefore, effective treatments for MS may require not only the mitigation of autoimmunity but also the stimulation of oligodendrocyte regeneration and restoration of a functional myelin sheath. Periodic cycles of prolonged fasting (PF) or of a fasting mimicking diet (FMD) lasting 2 or more

Multiple Sclerosis

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Protein restriction cycles reduce IGF-1 and phosphorylated Tau, and improve behavioral performance in an Alzheimer's disease mouse model

Edoardo Parrella,[1] Tom Maxim,[1] Francesca Maialetti,[2] Lu Zhang,[1] Junxiang Wan,[1] Min Wei,[1] Pinchas Cohen,[1] Luigi Fontana[3,4,5] and Valter D. Longo[1]

[1]Longevity Institute, Davis School of Gerontology, and Department of Biological Sciences, University of Southern California, Los Angeles, CA, USA
[2]Division of Nutrition and Aging, Istituto Superiore di Sanità, Rome, Italy
[3]Division of Geriatrics and Nutritional Science, Washington University in St. Louis St. Louis, MO, USA
[4]Department of Medicine, Salerno University School of Medicine, Salerno, Italy
[5]Healthy Aging Platform, CEINGE Biotecnologie Avanzate, Napoli, Italy

Summary

In laboratory animals, calorie restriction (CR) protects against aging, oxidative stress, and neurodegenerative pathologies. Reduced levels of growth hormone and IGF-1, which mediate some of the protective effects of CR, can also extend longevity and/or protect against age-related diseases in rodents and humans. However, severely restricted diets are difficult to maintain and are associated with chronically low weight and other major side effects. Here we show that 4 months of periodic protein restriction cycles (PRCs) with supplementation of nonessential amino acids in mice already displaying significant cognitive impairment and Alzheimer's disease (AD)-like pathology reduced circulating IGF-1 levels by 30–70% and caused an 8-fold increase in IGFBP-1. Whereas PRCs did not affect the levels of β amyloid (Aβ), they decreased tau phosphorylation in the hippocampus and alleviated the age-dependent impairment in cognitive performance. These results indicate that periodic protein restriction cycles without CR can promote changes in circulating growth factors and tau phosphorylation associated with protection against age-related neuropathologies.

Key words: aging; alzheimer; IGF-1; IGFBP-1; protein restriction; tau.

Introduction

Calorie restriction (CR) without malnutrition is effective in protecting the brain against aging and oxidative stress (Martin *et al.*, 2006). Several studies support a beneficial role for this dietary intervention in protecting against age-dependent decay in cognitive performance in rodents (Fontan-Lozano *et al.*, 2008). In addition, CR shows remarkable neuroprotective properties against neurodegenerative diseases including stroke, Parkinson's disease (PD), Huntington's disease (HD), and Alzheimer's disease (AD) in several animal models (Mattson, 2005; Patel *et al.*, 2005).

Recent studies in different AD mouse models reported that reducing food intake can diminish AD-related neuropathologies and cognitive dysfunction. For example, CR reduces the progression of β amyloid (Aβ) deposition in the hippocampus and cerebral cortex of mice carrying familial Alzheimer's disease mutations in the amyloid precursor protein (APP) and/or presenilin 1 (Patel *et al.*, 2005; Wang *et al.*, 2005; Mouton *et al.*, 2009). CR ameliorates neurodegenerative phenotypes assessed by object recognition and contextual fear conditioning tests and reduces tau hyperphosphorylation in cDKO (conditional double knockout) AD mice (Wu *et al.*, 2008). Mattson and coworkers have shown that CR can also ameliorate age-related memory impairment and decrease Aβ and phosphorylated tau accumulation in a triple transgenic mouse (3xTg-AD) model that overexpresses mutated human genes linked to AD (PS-1, APP) and frontotemporal dementia (tau) (Halagappa *et al.*, 2007). Furthermore, studies in human populations suggest that diet plays an important role in AD and reduced food intake may protect against this pathology. For example, an epidemiological study by Luchsinger and colleagues indicates that individuals with a low-calorie intake may have a reduced risk of developing AD (Luchsinger *et al.*, 2002).

Among the large number of metabolic and physiological changes caused by CR, the reduction in growth hormone (GH)/insulin-like factor (IGF-1) signaling may be important for its protective effects (Fontana *et al.*, 2010). Circulating IGF-1 is a hormone produced primarily by the liver that regulates energy metabolism, cell proliferation, cell differentiation, body size, and lifespan. IGF-1 levels are regulated by calorie and/or protein availability. Long-term CR decreases serum IGF-1 concentration by approximately 30–40% in rodents (Thissen *et al.*, 1994) but not in humans unless protein intake is also reduced (Fontana *et al.*, 2008). Mutations that decrease the activity of growth hormone (GH)/IGF-1 signaling, similarly to CR, can extend longevity and enhance stress resistance in a wide range of organisms and systems (Kenyon, 2005), including the mammalian central nervous system (CNS) (Parrella & Longo, 2010). Although the overlap between the pathways altered by these nutritional and genetic interventions seems to be only partial, it has been proposed that decline in IGF-1 levels can mediate part of the beneficial effects caused by CR (Sonntag *et al.*, 1999; Longo & Finch 2003). In support of this theory, it has been shown recently that reducing IGF-1 signaling in an AD mouse carrying APP and PS-1 mutations protects against Alzheimer's-like disease symptoms including cognitive deficits and neuroinflammation (Cohen *et al.*, 2009). Notably, GH receptor-deficient (GHRD) mice and humans are protected from major diseases (Ikeno *et al.*, 2009; Masternak *et al.*,

Correspondence
Valter D. Longo, Longevity Institute, Davis School of Gerontology, University of Southern California, 3715 McClintock Avenue, Los Angeles, CA 90089-0191, USA. Tel.: +1 213 7406212; fax: +1 213 8215714; e-mail: vlongo@usc.edu

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Article

Fasting-mimicking diet cycles reduce neuroinflammation to attenuate cognitive decline in Alzheimer's models

Priya Rangan,[1,13] Fleur Lobo,[1,13] Edoardo Parrella,[1,7,13] Nicolas Rochette,[9,10] Marco Morselli,[8,9] Terri-Leigh Stephen,[1] Anna Laura Cremonini,[5,6] Luca Tagliafico,[5] Angelica Persia,[5] Irene Caffa,[5] Fiammetta Monacelli,[5,6] Patrizio Odetti,[5,6] Tommaso Bonfiglio,[5] Alessio Nencioni,[5,6] Martina Pigliautile,[12] Virginia Boccardi,[12] Patrizia Mecocci,[12] Christian J. Pike,[1] Pinchas Cohen,[1,2] Mary Jo LaDu,[11] Matteo Pellegrini,[8,9] Kyle Xia,[1] Katelynn Tran,[1] Brandon Ann,[1] Dolly Chowdhury,[1] and Valter D. Longo[1,3,4,14,*]

[1]Longevity Institute, School of Gerontology, Department of Biological Sciences, University of Southern California, 3715 McClintock Avenue, Los Angeles, CA 90089-0191, USA
[2]USC Dornsife College of Letters, Arts & Sciences, Department of Biological Sciences, University of Southern California, 3551 Trousdale Pkwy., Los Angeles, CA 90089-0191, USA
[3]Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC, Keck School of Medicine, University of Southern California, 1425 San Pablo St., Los Angeles, CA 90033, USA
[4]IFOM FIRC Institute of Molecular Oncology, Via Adamello 16, Milano, MI 20139, Italy
[5]Department of Internal Medicine and Medical Specialties, University of Genoa, Viale Benedetto XV 6, Genova, GE 16132, Italy
[6]IRCCS Ospedale Policlinico San Martino, Largo Rosanna Benzi 10, 16132 Genoa, Italy
[7]Department of Molecular and Translational Medicine, University of Brescia, Viale Europa 11, Brescia, BS 25123, Italy
[8]Department of Molecular, Cell and Developmental Biology, University of California, Los Angeles, 610 Charles E. Young Dr. S., Los Angeles, CA 90095, USA
[9]Institute for Quantitative and Computational Biosciences, University of California, Los Angeles, 611 Charles E. Young Dr. E., Los Angeles, CA 90095, USA
[10]Department of Ecology and Evolutionary Biology, University of California, Los Angeles, 612 Charles E. Young Dr. E., Los Angeles, CA 90095, USA
[11]Department of Anatomy and Cell Biology, University of Illinois at Chicago, Chicago, IL, USA
[12]Santa Maria della Misericordia Hospital, Section of Gerontology and Geriatrics, Department of Medicine and Surgery, University of Perugia, Perugia, Italy
[13]These authors contributed equally
[14]Lead contact
*Correspondence: vlongo@usc.edu
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SUMMARY

The effects of fasting-mimicking diet (FMD) cycles in reducing many aging and disease risk factors indicate it could affect Alzheimer's disease (AD). Here, we show that FMD cycles reduce cognitive decline and AD pathology in E4FAD and 3xTg AD mouse models, with effects superior to those caused by protein restriction cycles. In 3xTg mice, long-term FMD cycles reduce hippocampal Aβ load and hyperphosphorylated tau, enhance genesis of neural stem cells, decrease microglia number, and reduce expression of neuroinflammatory genes, including superoxide-generating NADPH oxidase (Nox2). 3xTg mice lacking Nox2 or mice treated with the NADPH oxidase inhibitor apocynin also display improved cognition and reduced microglia activation compared with controls. Clinical data indicate that FMD cycles are feasible and generally safe in a small group of AD patients. These results indicate that FMD cycles delay cognitive decline in AD models in part by reducing neuroinflammation and/or superoxide production in the brain.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease characterized by the accumulation of amyloid-beta (Aβ) via Aβ oligomers (oAβ) that can be toxic in their fibrillar form (Gong et al., 2003) or aggregate to form amyloid plaques and promote the generation of hyperphosphorylated tau protein (Bloom, 2014). This distinct neuropathology can lead to inflammation and oxidative damage, synaptic degeneration, and neuronal death, ultimately affecting the learning and memory functions of the cerebral cortex and hippocampus (Cline et al., 2018). The 3xTg-AD mouse model (3xTg) exhibits both Aβ and tau pathology, characteristic of the human disease (Oddo et al., 2003; Sterniczuk et al., 2010). In contrast, the EFAD-Tg mouse model (Youmans et al., 2012) can have different human *APOE* alleles (*APOE2*, *APOE3*, *APOE4*) knocked into the 5xFAD-Tg mice (Oakley et al., 2006),

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RESEARCH ARTICLE

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Efficacy of a fasting-mimicking diet in functional therapy for depression: A randomised controlled pilot trial

Giuseppe Maniaci[1] | Caterina La Cascia[1] | Alessandra Giammanco[1] | Laura Ferraro[1] | Roberta Chianetta[2] | Roberta Di Peri[1] | Zaira Sardella[1] | Roberto Citarrella[2] | Yuri Mannella[1] | Stefania Larcan[1] | Simonetta Montana[1] | Mario G. Mirisola[3] | Valter Longo[4,5] | Manfredi Rizzo[2] | Daniele La Barbera[1]

[1]Section of Psychiatry, Department of Biomedicine, Neurosdence, and Advanced Diagnostic (BIND), University of Palermo, Palermo, Italy

[2]Department of Health Promotion, Mother, and Child Care, Internal Medicine and Medical Specialties, (PROMISE), University of Palermo, Palermo, Italy

[3]Department of Surgical, Oncological, and Oral Sciences, University of Palermo, Palermo, Italy

[4]Department of Biological Sciences, Longevity Institute, Davis School of Gerontology, University of Southern California, Los Angeles, California

[5]IFOM FIRC Institute of Molecular Oncology, Milan, Italy

Correspondence
Giuseppe Maniaci, Section of Psychiatry, Department of Biomedicine, Neuroscience, and Advanced Diagnostic (BIND), University of Palermo, Via del Vespro 129, 90127 Palermo, Italy.
Email: giuseppe.maniaci02@unipa.it

Abstract

Objective: This randomized controlled trial examined the efficacy of adding a fasting-mimicking diet to a structured psychotherapy protocol for treating depression.

Design: Of 20 patients with depression, 10 were randomly assigned to psychotherapy and dieting (i.e., experimental group) and the other 10 to psychotherapy only (i.e., control group). Patients in both groups received 20 individual sessions of functional therapy along with nutrition consultation. Patients in the control group were instructed to maintain their usual daily diets.

Results: Both treatments were effective in reducing depression as well as increasing self-esteem and quality of life. The experimental group showed improved self-esteem and psychological quality of life as well as a reduction in their mean body mass index, in comparison to the control group.

Giuseppe Maniaci and Caterina La Cascia equally contributed to this work; they both are first authors of the study.

ClinicalTrials.gov ID: NCT04050475

Depression

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