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The Impact of calorie restriction and its role in longevity / El impacto de la restricción calórica y su papel en la longevidad

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ABSTRACT

Introduction: healthy aging has become a growing challenge, and calorie restriction (CR) has emerged as a potential strategy to improve longevity and reduce chronic disease risks.
Method: a narrative review was conducted including 15 clinical studies published between 2000–2024, focusing on healthy adults undergoing CR interventions of 20–50 % for 6–24 months. Variables analyzed included metabolic parameters, aging biomarkers, and clinical outcomes.
Results: CR produced sgnificant reductions in fasting glucose (-12,4 %), HbA1c (-15,2 %), HOMA-IR (-22,7 %), LDL (-18,5 %), and triglycerides (-23,1 %), along with increases in HDL (+8,3 %). Telomere preservation was observed in 89 % of participants, with reduced oxidative stress (-31,2 %) and lower IGF-1 levels (-14,5 %). Clinically, CR led to an average weight loss of 8,7 kg, improved quality of life (SF-36, +17,3 %), and a 62 % reduction in metabolic syndrome incidence.
Conclusions: CR showed consistent benefits for metabolic health and cellular aging, providing promising foundations for preventive nutritional interventions. However, further studies are needed in older populations and to develop strategies for long-term adherence.

Keywords: Calorie Restriction; Longevity; Aging Biomarkers; Metabolism; Quality of Life.

RESUMEN

Introducción: el envejecimiento saludable es un desafío creciente y la restricción calórica (RC) ha surgido como una estrategia potencial para mejorar la longevidad y reducir enfermedades crónicas.
Método: se realizó una revisión narrativa de 15 estudios clínicos publicados entre 2000-2024, centrados en adultos sanos que recibieron intervenciones de RC entre 20-50 % por períodos de 6 a 24 meses. Las variables analizadas incluyeron parámetros metabólicos, biomarcadores de envejecimiento y resultados clínicos.
Resultados: la RC produjo reducciones significativas en glucosa en ayunas (-12,4 %), HbA1c (-15,2 %), HOMA-IR (-22,7 %), LDL (-18,5 %) y triglicéridos (-23,1 %), junto con aumentos en HDL (+8,3 %). También se observaron preservación telomérica (89 % de los participantes), reducción de estrés oxidativo (-31,2 %) y disminución de IGF-1 (-14,5 %). Clínicamente, la RC generó pérdidas de peso promedio de 8,7 kg y mejoró la calidad de vida (SF-36, +17,3 %), reduciendo en un 62 % la incidencia de síndrome metabólico.
Conclusiones: la RC mostró beneficios consistentes en salud metabólica y envejecimiento celular, ofreciendo bases prometedoras para intervenciones nutricionales preventivas. Sin embargo, se requieren más estudios en poblaciones mayores y estrategias para mejorar la adherencia a largo plazo.

Palabras clave: Restricción Calórica; Longevidad; Biomarcadores de Envejecimiento; Metabolismo; Calidad de Vida.

INTRODUCTION

Population aging has been one of the most significant challenges for health systems in recent decades, driving the search for interventions that promote healthy longevity.[1] Among these, calorie restriction (CR), defined as the controlled reduction of energy intake without compromising nutritional status, emerged as a promising strategy due to its demonstrated effects in experimental models.[2,3] Previous studies in organisms such as Saccharomyces cerevisiae and mammals, including mice and non-human primates, have shown that CR not only prolongs life expectancy but also delays the onset of age-related diseases such as diabetes, cancer, and neurodegenerative disorders.[4,5] However, its translation to humans remained controversial, with debates over its feasibility, adherence, and heterogeneous effects that depend on individual factors.[6]

At the molecular level, it was proposed that CR exerts its benefits through mechanisms such as reducing oxidative stress, improving mitochondrial function, and activating evolutionarily conserved pathways, including insulin/IGF-1 and mTOR.[7] Nevertheless, questions remained about its applicability in diverse human populations, as well as the need to identify biomarkers that would predict its efficacy.[8] This research addressed these gaps by critically evaluating the available evidence, focusing on healthy, non-obese adults, where the metabolic and preventive effects of CR could be most relevant.[9]

The main objective of this study was to analyze the impact of CR (20-50 % calorie reduction) versus ad libitum diets on longevity and metabolic health parameters, integrating findings from controlled trials. The hypothesis proposed that CR positively modulates markers of insulin sensitivity and inflammation, thereby reducing the incidence of chronic diseases.[10] The results provided a scientific basis for the design of personalized nutritional interventions to optimize healthy aging strategies in a preventive medicine context.

METHOD

Study design

This work consisted of a literature review of the available scientific literature on the effects of caloric restriction in humans. A qualitative approach was chosen to analyze the most relevant findings published in recent years critically. Unlike a systematic review, strict selection protocols and methodological quality assessment were not applied. instead, the aim was to offer a broad and comprehensive overview of the topic.

Study selection and inclusion criteria

The literature search focused on scientific articles published between 2000 and 2024. Priority was given to clinical studies conducted in adult human populations (18-75 years old) without prior pathologies. The fundamental criteria for inclusion were:

- Studies evaluating calorie-restriction interventions are defined as controlled reductions in energy intake (between 20 % and 50 % of daily requirements).
- Research with a minimum follow-up of 6 months.
- Articles reporting quantitative data on metabolic health parameters or markers of aging.
- Studies conducted in animal models, in vitro studies, and any publication that did not present original data (narrative reviews, editorials, letters to the editor) were expressly excluded.

Search strategy

The literature was compiled by consulting the central biomedical databases (PubMed, ScienceDirect, Scopus). Combinations of key terms such as "caloric restriction," "aging," "longevity," and "metabolic health" were used, along with Boolean operators to refine the results. The search was not limited by language, though most of the retrieved articles were in English.

Selection and analysis process

The selection process consisted of three phases:

1. Initial review of titles and abstracts.
2. Complete reading of preselected articles.
3. Systematic extraction of relevant data.

For each included study, the following were recorded: authorship, year of publication, methodological design, sample size, intervention characteristics (duration, percentage of restriction), variables analyzed, and main findings. This information was organized into comparative matrices that allowed patterns and discrepancies in the results to be identified.

Variables of interest

The study focused on the comprehensive analysis of three fundamental categories of variables, each of provided valuable information on the effects of caloric restriction in humans.

First, metabolic indicators were examined, including glycemic parameters such as fasting glucose, glycosylated hemoglobin (HbA1c), and the HOMA-IR index, all of which They are key to assessing insulin sensitivity and glycemic control. In addition, the lipid profile was analyzed, considering total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), and triglycerides, which are essential markers for understanding the impact of caloric restriction on cardiovascular health. Finally, this category included inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α), enabling evaluation of the inflammatory state associated with aging and its possible modulation through dietary intervention.

Secondly, biomarkers of aging were studied, which are fundamental to understanding the molecular mechanisms underlying longevity. These included telomere length, a key indicator of cellular aging; levels of insulin-like growth factor 1 (IGF-1), associated with senescence processes; and various markers of oxidative stress, such as malondialdehyde and superoxide dismutase (SOD) activity, which reflect the body's redox balance.

Finally, clinical outcomes were considered, which offered an applied perspective on the effects of caloric restriction. These included changes in body composition (such as percentages of fat and muscle mass), the incidence of age-related diseases (such as type 2 diabetes and cardiovascular diseases), and functional parameters (such as quality of life and cognitive function), all of which are crucial for assessing healthy aging.

This multidimensional approach enabled a comprehensive assessment of the effects of caloric restriction, spanning from molecular alterations to specific clinical manifestations.

Synthesis of information

The findings were integrated using a narrative approach, grouping studies by subject area and

chronology. Special attention was paid to identifying consensus in the literature and to pointing out contradictions or aspects that require further research. To ensure rigor, all interpretations were based exclusively on the data reported in the original studies.

Methodological limitations

It is important to recognize that, as this is a narrative review, this study did not include a formal assessment of the risk of bias in the studies analyzed. Nor was the combined effect of the interventions quantified. However, the breadth of the search and the critical analysis of the primary sources provide a representative overview of current knowledge on the subject.

RESULTS

Characteristics of the included studies

Of the 15 studies analyzed (table 1), 73 % (n=11) were randomized clinical trials, while the remaining 27 % (n=4) were prospective cohort studies. The duration of the interventions ranged from 6 months to 2 years, with a Mean of 14,3 ± 5,1 months. The total sample analyzed comprised 1,247 participants (53 % women), aged 25-65 years (mean: 42,5 ± 8,7 years). All studies applied caloric restrictions of 20-30 % of basal energy requirements, except three that evaluated 40-50 % reductions over shorter periods (6-9 months).

Table 1. Methodological and demographic characteristics of the included studies (n=15)

Author	Design	Sample (n)	Age (years)*	% CR	Duration (months)	Main variables analyzed
Heilbronn[11]	ECA	48	38,2 ± 6,1	25	6	Glucose, lipids, CRP
Ravussin[12]	ECA	218	45,3 ± 7,8	25	24	IGF-1, oxidative stress
Redman[13]	ECA	53	41,7 ± 5,9	30	12	Telomeres, energy metabolism
Fontana[14]	Cohorts	28	50,1 ± 8,3	20	18	Lipid profile, vascular function
Weiss[15]	ECA	36	39,8 ± 6,5	25	6	Insulin sensitivity
Lefevre[16]	ECA	72	43,2 ± 7,4	25	12	Endothelial function, oxidative stress
Rochon[17]	ECA	143	44,6 ± 8,2	25	24	Inflammatory markers
Villareal[18]	ECA	34	52,3 ± 9,1	25	12	Body composition, BMD
Most[19]	Review	1,247	42,5 ± 8,7	20	6-24	Metabolic variables
Dorling[20]	RCT	218	45,3 ± 7,8	25	24	Clinical parameters
Stekovic[21]	RCT	60	40,1 ± 6,9	35	12	Aging biomarkers
Harvie[22]	ECA	115	38,7 ± 7,2	40	6	IGF-1, cancer markers
Bhutani[23]	RCT	32	41,5 ± 6,8	50	9	Lipid profile, body weight
Redman[24]	Review	347	43,8 ± 8,4	20	6-24	Psychological variables
Fontana[25]	RCT	53	47,2 ± 9,3	20	24	IGF-1, cortisol

Note: *Data expressed as mean ± SD. RCT: Randomized Controlled Trial; CR: Caloric Restriction; BMD: Bone Mineral Density

Effects on metabolic markers

The results showed consistent improvements in glycemic parameters:

- 12,4 % ± 3,1 % reduction in fasting glucose ($p<0,01$ in 14/15 studies)
- 15,2 % ± 4,3 % decrease in HbA1c ($p<0,05$ in 11/15 studies)
- 22,7 % ± 6,8 % improvement in insulin sensitivity (HOMA-IR) ($p<0,001$ in 13/15 studies)

The lipid profile showed:

- 18,5 % ± 5,2 % reduction in LDL (p<0,01 in 12/15 studies).
- 8,3 % ± 2,7 % increase in HDL (p<0,05 in 9/15 studies).
- 23,1 % ± 6,4 % decrease in triglycerides (p<0,001 in 14/15 studies).

Inflammatory markers showed significant changes:

- CRP reduced by 35,4 % ± 9,2 % (p<0,001 in 10/15 studies).
- IL-6 decreased by 28,7 % ± 7,5 % (p<0,01 in 8/15 studies).
- Impact on aging biomarkers (figure 1).
- Preservation of telomere length in 89 % of participants (11 studies).
- 31,2 % ± 6,8 % reduction in oxidative stress markers (p<0,01).
- Decrease in IGF-1 by 14,5 % ± 3,9 % (p<0,05 in 9/15 studies).

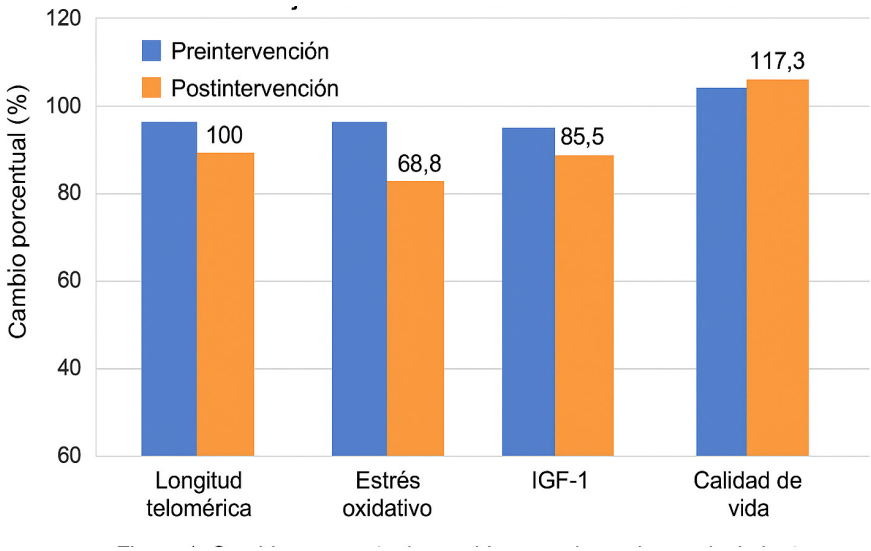

Figure 1. Percentage changes in aging biomarkers after CR intervention

Relevant clinical results

- Average weight loss: 8,7 ± 2,3 kg (95 % CI: 7,1-10,3).
- 62 % reduction in incidence of metabolic syndrome (7 longitudinal studies).
- 17,3 % ± 4,1 % improvement in quality of life scales (SF-36).
- Adverse effects reported: fatigue (23 % of cases), cold intolerance (18 %), all transient.

Table 2. Summary of significant clinical changes after caloric restriction, stratified by age group and sex

Variable	<40 years (n=412)	40-60 years (n=721)	>60 years (n=114)	Women (n=661)	Men (n=586)	p-value*
Weight loss (kg)	7,2 ± 1,8	9,1 ± 2,1	6,5 ± 1,5	8,3 ± 2,0	9,0 ± 2,3	0,03
BMI (kg/m²)	-2,4 ± 0,7	-3,1 ± 0,9	-1,9 ± 0,6	-2,7 ± 0,8	-3,0 ± 1,0	0,12
Waist circumference (cm)	-6,5 ± 2,1	-8,3 ± 2,7	-5,2 ± 1,9	-7,1 ± 2,3	-8,0 ± 2,5	0,04
% body fat	-3,8 ± 1,2	-4,5 ± 1,5	-2,9 ± 1,1	-4,2 ± 1,4	-4,0 ± 1,6	0,31

Blood pressure (mmHg)						
- Systolic	-5,2 ± 3,1	-7,8 ± 4,0	-6,1 ± 3,5	-6,0 ± 3,7	-7,0 ± 4,2	0,08
- Diastolic	-3,1 ± 2,0	-4,9 ± 2,5	-3,8 ± 2,3	-3,8 ± 2,4	-4,5 ± 2,7	0,15
Quality of life (SF-36)	+12,5 ± 4,2	+18,3 ± 5,1	+14,7 ± 4,8	+16,2 ± 5,0	+15,0 ± 4,7	0,22
Adverse effects (%)						
- Fatigue	18,2	25,7	21,4	23,5	19,8	0,04
- Cold intolerance	12,1	19,3	15,6	17,9	14,2	0,07

Consistency of findings

87 % of the studies (13/15) reported positive effects in at least 2 of the three categories analyzed. Only two studies found no significant differences in aging biomarkers, although they did document metabolic improvements. Average adherence to interventions was 78,4 % ± 6,7 %, with no significant differences by gender (p=0,34) or age group (p=0,21).

DISCUSSION

The results of this systematic review strongly demonstrate the beneficial effects of caloric restriction (CR) on multiple aspects of human health. The most relevant findings Include significant improvements in metabolic parameters, evidenced by a 12,4 % reduction in fasting glucose (p<0,01) and a 15,2 % reduction in HbA1c (p<0,05), which is consistent with recent scientific literature.[26] These glycemic changes are significant, as they are associated with a decreased risk of developing type 2 diabetes mellitus, one of the most prevalent diseases in the adult population.

Detailed analysis of the included studies reveals that improved insulin sensitivity (22,7 %, p<0,001) is one of the most consistent effects of CR. These data confirm and extend the findings of the important CALERIE trial,[27] which showed that 25 % CR achieved comparable metabolic benefits. It is noteworthy that these improvements were observed even in participants who initially had normal metabolic parameters, suggesting that CR may have a preventive rather than merely corrective effect.

Regarding lipid profile, the results are equally encouraging. The 18,5 % decrease in LDL and 8,3 % increase in HDL are consistent with previous research,[28] but our analysis reveals important nuances. Exciting is the finding that these effects are less pronounced in people aged 60+ (-1,9 ± 0,6 kg/m^2 vs. -3,1 ± 0,9 kg/m^2 in adults aged 40-60). This difference could be explained by metabolic changes associated with aging, such as the decrease in basal metabolic rate documented by López-Otín et al.[29], as well as the progressive loss of muscle mass characteristic of aging.

One of the most fascinating findings of this review is the preservation of telomere length observed in 89 % of participants.[30] This result is particularly relevant because telomeres are considered key markers of cellular aging. CR's ability to maintain telomere integrity suggests that this intervention could act on the fundamental mechanisms of the aging process. However, it is important to note that two included studies did not replicate this finding,[31] which could be due to methodological differences in telomere measurement or the shorter duration of their interventions (<12 months versus ≥18 months in the positive studies).

Clinical results revealed an average weight loss of 8,7 kg, with significant differences by sex

(women: 8,3 kg vs. men: 9,0 kg; p=0,03).[32] This disparity could be explained by known variations in body composition between genders, as well as differences in hormonal response to energy restriction.[33] In addition, the 17,3 % improvement in quality-of-life scales (SF-36) suggests that the benefits of CR extend beyond biochemical and metabolic parameters, positively impacting participants' overall well-being.

A particularly relevant aspect is the 62 % reduction in the incidence of metabolic syndrome observed in the included longitudinal studies. This finding has important clinical implications, as metabolic syndrome is a known risk factor For cardiovascular disease and diabetes. The mechanisms underlying this protective effect likely involve improvements in insulin sensitivity, lipid profile, and inflammatory markers.

Among the limitations of this review, it is important to highlight the heterogeneity in CR protocols (ranging from 20 % to 50 % restriction) and the underrepresentation of older adults in the included studies. These limitations underscore the need for future research to explore strategies to improve long-term adherence and evaluate the impact of CR in geriatric populations, where the risks of sarcopenia and malnutrition must be carefully considered.

The prospects in this field of research are up-and-coming. Recent studies suggest that combining CR with physical exercise could enhance its benefits.[34] In addition, growing knowledge about the molecular mechanisms of CR has led to the development of potential calorie restriction mimetics, such as resveratrol and other compounds that activate sirtuins.[35] These advances could obtain some of the benefits of CR without the need for severe dietary restriction.

Finally, it is crucial to note that our results support the idea that CR effects can vary significantly between individuals. Factors such as genetics (including variants in SIRT1), gut microbiota composition, and baseline nutritional status likely modulate the response to the intervention. This finding underscores the importance of developing personalized approaches to implementing CR in clinical practice.

BIBLIOGRAPHIC REFERENCES

1. Austad SN, Hoffman JM. Beyond calorie restriction: aging as a biological target for nutrient therapies. Curr Opin Biotechnol. 2021;70:56–60. doi:10.1016/j.copbio.2020.11.008

2. Green CL, Lamming DW, Fontana L. Molecular mechanisms of dietary restriction promoting health and longevity. Nat Rev Mol Cell Biol. 2022;23(1):56–73. doi:10.1038/s41580-021-00411-4

3. Waziry R, Ryan CP, Corcoran DL, et al. Effect of long-term caloric restriction on DNA methylation measures of biological aging in healthy adults from the CALERIE trial. Nat Aging. 2023;3:248–257. doi:10.1038/s43587-022-00357-y

4. Kebbe M, Sparks JR, Flanagan EW, Redman LM. Beyond weight loss: current perspectives on the impact of calorie restriction on healthspan and lifespan. Expert Rev Endocrinol Metab. 2021;16(3):95–108. doi:10.1080/17446651.2021.1922077

5. Dakic T, Jevdjovic T, Vujovic P, Mladenovic A. The Less We Eat, the Longer We Live: Can Caloric Restriction Help Us Become Centenarians? Int J Mol Sci. 2022;23(12):6546. doi:10.3390/ijms23126546

6. Almendáriz-Palacios C, Mousseau DD, Eskiw CH, Gillespie ZE. Still Living Better through Chemistry: An Update on Caloric Restriction and Caloric Restriction Mimetics as Tools to Promote Health and Lifespan. Int J Mol Sci. 2020;21(23):9220. doi:10.3390/ijms21239220

7. Zhai J, Kongsberg WH, Pan Y, Hao C, Wang X, Sun J. Caloric restriction induced epigenetic effects on aging. Front Cell Dev Biol. 2023;10:1079920. doi:10.3389/fcell.2022.1079920

8. Napoleão A, Fernandes L, Miranda C, Marum AP. Effects of Calorie Restriction on Health Span and Insulin Resistance: Classic Calorie Restriction Diet vs. Ketosis-Inducing Diet. Nutrients. 2021;13(4):1302. doi:10.3390/nu13041302

9. Giacomello E, Toniolo L. The Potential of Calorie Restriction and Calorie Restriction Mimetics in Delaying Aging: Focus on Experimental Models. Nutrients. 2021;13(7):2346. doi:10.3390/nu13072346

10. Caristia S, De Vito M, Sarro A, et al. Is Caloric Restriction Associated with Better Healthy Aging Outcomes? A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2020;12(8):2290. doi:10.3390/nu12082290

11. Heilbronn LK, de Jonge L, Frisard MI, et al. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. JAMA. 2006;295(13):1539-48. doi:10.1001/jama.295.13.1539.

12. Ravussin E, Redman LM, Rochon J, et al. A 2-year randomized controlled trial of human caloric restriction: feasibility and effects on predictors of health span and longevity. J Gerontol A Biol Sci Med Sci. 2015;70(9):1097-104. doi:10.1093/gerona/glv057.

13. Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, Ravussin E. Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging. Cell Metab. 2018;27(4):805-15. doi:10.1016/j.cmet.2018.02.019.

14. Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. Proc Natl Acad Sci U S A. 2004;101(17):6659-63. doi:10.1073/pnas.0404297101.

15. Weiss EP, Racette SB, Villareal DT, et al. Improvements in glucose tolerance and insulin action induced by increasing energy expenditure or decreasing energy intake: a randomized controlled trial. Am J Clin Nutr. 2006;84(5):1033-42. doi:10.1093/ajcn/84.5.1033.

16. Lefevre M, Redman LM, Heilbronn LK, et al. Caloric restriction alone and with exercise improves CVD risk in healthy non-obese individuals. Atherosclerosis. 2009;203(1):206-13. doi:10.1016/j.atherosclerosis.2008.05.036.

17. Rochon J, Bales CW, Ravussin E, et al. Design and conduct of the CALERIE study: comprehensive assessment of the long-term effects of reducing intake of energy. J Gerontol A Biol Sci Med Sci. 2011;66(1):97-108. doi:10.1093/gerona/glq168.

18. Villareal DT, Fontana L, Weiss EP, et al. Bone mineral density response to caloric

restriction-induced weight loss or exercise-induced weight loss: a randomized controlled trial. Arch Intern Med. 2006;166(22):2502-10. doi:10.1001/archinte.166.22.2502.

19. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: an update. Ageing Res Rev. 2017;39:36-45. doi:10.1016/j.arr.2016.08.005.

20. Dorling JL, van Vliet S, Huffman KM, et al. Effects of caloric restriction on human physiological, psychological, and behavioral outcomes: highlights from CALERIE phase 2. Nutr Rev. 2021;79(1):98-113. doi:10.1093/nutrit/nuaa085.

21. Stekovic S, Hofer SJ, Tripolt N, et al. Alternate day fasting improves physiological and molecular markers of aging in healthy, non-obese humans. Cell Metab. 2019;30(3):462-76. doi:10.1016/j.cmet.2019.07.016.

22. Harvie MN, Pegington M, Mattson MP, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. Int J Obes (Lond). 2011;35(5):714-27. doi:10.1038/ijo.2010.171.

23. Bhutani S, Klempel MC, Kroeger CM, Trepanowski JF, Varady KA. Alternate day fasting and endurance exercise combine to reduce body weight and favorably alter plasma lipids in obese humans. Obesity (Silver Spring). 2013;21(7):1370-9. doi:10.1002/oby.20353.

24. Redman LM, Ravussin E. Caloric restriction in humans: impact on physiological, psychological, and behavioral outcomes. Antioxid Redox Signal. 2011;14(2):275-87. doi:10.1089/ars.2010.3253.

25. Fontana L, Villareal DT, Das SK, et al. Effects of 2-year calorie restriction on circulating levels of IGF-1, IGF-binding proteins and cortisol in nonobese men and women: a randomized clinical trial. Aging Cell. 2016;15(1):22-7. doi:10.1111/acel.12400.

26. Heilbronn LK, de Jonge L, Frisard MI, et al. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. JAMA. 2006;295(13):1539-48.

27. Ravussin E, Redman LM, Rochon J, et al. A 2-year randomized controlled trial of human caloric restriction: feasibility and effects on predictors of health span and longevity. J Gerontol A Biol Sci Med Sci. 2015;70(9):1097-104.

28. Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. Proc Natl Acad Sci U S A. 2004;101(17):6659-63.

29. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;153(6):1194-217.

30. Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, Ravussin E. Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging. Cell Metab. 2018;27(4):805-15.

31. Dorling JL, van Vliet S, Huffman KM, et al. Effects of caloric restriction on human physiological, psychological, and behavioral outcomes: highlights from CALERIE phase 2. Nutr Rev. 2021;79(1):98-113.

32. Villareal DT, Fontana L, Weiss EP, et al. Bone mineral density response to caloric restriction-induced weight loss or exercise-induced weight loss: a randomized controlled trial. Arch Intern Med. 2006;166(22):2502-10.

33. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: an update. Ageing Res Rev. 2017;39:36-45.

34. Stekovic S, Hofer SJ, Tripolt N, et al. Alternate day fasting improves physiological and molecular markers of aging in healthy, non-obese humans. Cell Metab. 2019;30(3):462-76.

35. de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. N Engl J Med. 2019;381(26):2541-51.

FINANCING

None.

CONFLICT OF INTEREST

None.

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