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Intermittent fasting: a strategy to counteract aging linked to oxidative stress

Ayuno intermitente: una estrategia para contrarrestar el envejecimiento vinculado al estrés oxidativo

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Abstract:

Aging is a multifactorial deterioration process that occurs in the life of an organism, which seems to be linked to oxidative stress. Intermittent fasting (IF) consists of food restriction with intermediate periods of regular food intake repeatedly. Various studies in human beings and experimental animal models have shown that intermittent fasting counteracts various alterations associated with age and weight loss, a decrease in the concentration of insulin, glucose, and serum lipids, and oxidative stress, improving antioxidant defense. This review summarizes the evidence available to date in PubMed to analyze the effects of IF on the aging process and its link with oxidative stress. The results suggested that food restriction on alternate days and with a time restriction improves aging processes by decreasing oxidative stress markers and increasing autophagy related to longevity. IF represents a promising non-pharmacological alternative to improve health in the adult population. However, more studies are required to know the chronic effect of fasting and recognize its effects as a therapy in diseases associated with aging.

Keywords:

Autophagy, intermittent fasting, aging, oxidative stress, caloric restriction

Resumen:

El envejecimiento es un proceso de deterioro multifactorial que ocurre en la vida de un organismo, el cual parece estar vinculado con el estrés oxidativo. El ayuno intermitente (AI) consiste en la restricción de alimentos con periodos intermedios de ingesta normal de alimentos de forma recurrente. Diversos estudios en seres humanos y modelos animales de experimentación han demostrado que el ayuno intermitente contrarresta varias alteraciones asociadas con la edad además de la pérdida de peso, la disminución en la concentración de insulina, glucosa y lípidos séricos y el estrés oxidativo, mejorando la defensa antioxidante. La presente revisión resume la evidencia disponible a la fecha en PubMed para analizar los efectos del (AI) en el proceso de envejecimiento y su vinculación con el estrés oxidativo. Los resultados sugieren que la restricción de alimentos en días alternos y con restricción de tiempo mejoran los procesos del envejecimiento al disminuir los marcadores del estrés oxidativo, y aumentar la autofagia que se relaciona con la longevidad. El AI representa una alternativa no farmacológica prometedora para mejorar la salud en población adulta. Sin embargo, se requieren de más estudios en población para conocer el efecto crónico del ayuno y reconocer sus efectos como terapia en enfermedades asociadas al envejecimiento.

***Palabras Clave**:*

Autofagia, ayuno intermitente, envejecimiento, estrés oxidativo, restricción calórica

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Introduction

Aging refers to a multifactorial process characterized by the accumulation of degenerative processes that involve multiple alterations in different molecular pathways. Numerous molecular pathways associated with longevity have been explored in other organisms.[1]Although understanding aging mechanisms is complex, it seems clear that oxidative stress and its effects are involved in aging.[2] Permanent or periodic reduction of caloric intake without malnutrition has been suggested to be a reliable strategy for life expectancy in mammals,[3] oxidative stress, and metabolic status, in addition to better cognition and a decrease in cardiovascular risk in obese and non-obese subjects.[4] Fasting, considered the restriction of food and beverages in a specific time, has been practiced throughout human existence in some cultures as a religious practice by Muslims, Christians, Buddhists, and others.[5] Intermittent fasting (IF) is considered an eating pattern with little or no energy intake with intermediate periods of regular food intake regularly. There are two general types of intermittent fasting, alternate-day fasting (ADF) and time-restricted feeding (TRF). The first consists of 24-hour fasts where only *ad libitum* water and food are provided for 24 hours. This pattern can be repeated five days a week with two days of fasting (5:2). In time-restricted fasts, consider abstinence alternating with feeding periods, for example, 8/16 hours.[6,7] Studies in animal models have shown that IF reduces oxidative stress and damage, inflammation promotes autophagy, improves energy metabolism, and benefits the intestinal microbiome.[8–10] Human studies with IF regimens have shown significant health effects in decreasing obesity, hypertension, asthma, rheumatoid arthritis, and diseases that develop more frequently with aging.[9,11] The review summarizes the beneficial results of practicing intermittent fasting to counteract aging and its relationship with oxidative stress, focusing on human intervention studies. Still, significant evidence in animal models is also described. Scientific articles were selected, including systematic reviews, meta-analyses, and original papers in PubMed published between 2000 and 2021. The review article was carried out from August to December 2021 and was carried out using the following keywords "intermittent fasting, aging, stress oxidative".

Adaptive responses to fasting

The human body, after 12 to 24 hours of fasting, results in a decrease in serum glucose and the depletion of the hepatic glycogen store, accompanied by the activation of gluconeogenesis; which is the utilization of non-glucosidic metabolites through fat-derived ketogenesis or branched-chain amino acids (leucine, isoleucine, and valine) as energy sources. Most organs, except the brain, can use fatty acids for energy; However, 3-hydroxybutyrate is converted to Acetyl-CoA to be used in the brain as an energy source during prolonged periods of fasting.[5] In recent years, interventions have been carried out to evaluate cellular metabolism, which is considered to have an essential role in the aging process. The decrease in branched-chain amino acids reduces adiposity and improves glucose tolerance in mice,[12] in addition to possessing protective properties against aging, extending the lifespan of progeroid mice.[13]

Various studies in humans have shown multiple benefits of IF on metabolism. Recently, the evaluation of older adults over 60 years of age, after 36 months of follow-up with regular IF, showed a reduction in body weight, insulin, and fasting glucose.[14] In a study of four young people without obesity with a prolonged fast of 58 hours, they evidenced by mass spectrometry the presence of various metabolites, including an increase in gluconeogenic metabolites, the pentose pathway, and antioxidants.[15] In another study, obese patients who had a high and low-fat diet accompanied by ADF for eight weeks decreased body weight and body fat and triglycerides, total cholesterol, and low-density lipoprotein (LDL), while high-density lipoprotein (HDL), blood pressure, remained unchanged.[16] Recently, a proteomic analysis in plasma of women aged 35-70 years with overweight or obesity, after having an ADF for 8 weeks, there is an increase in apolipoprotein A4 (APOA4) and a decrease in apolipoprotein C2 (APOC2) and C3 (APOC3), which was correlated with the significant reduction in serum triglycerides, suggesting that IF has a positive effect on lipid metabolism.[17]

Similarly, subjects with prolonged fasting of 10 days and a caloric intake of 250 kcal/day improve metabolic biomarkers (decrease in glucose and serum insulin, glycosylated hemoglobin, total cholesterol, LDL and triglycerides, and an increase in HDL).[18] Stekovic *et al.* (2019) evaluated subjects without obesity with ADF for four weeks, reduced body fat, serum LDL cholesterol, increased 3-hydroxybutyrate, polyunsaturated fatty acids, improving cardiovascular health.[19]Although a meta-analysis study and a recent systematic review coincide in indicating that few studies have shown a limited decrease in the lipid profile after an IF regimen, it is clear that anthropometry, body composition, and lipid profile benefit in subjects with overweight or obesity in the same magnitude as caloric restriction.[20,21]

Likewise, the beneficial effects of IF have been evidenced by improving various metabolic biomarkers in experimental animals. In a study in C57BL/6 mice with an ADF regimen, serum glucose and insulin levels were lowered, and 3-hydroxybutyrate levels increased, compared to the *ad libitum* fed group and the 40% calorie-restricted group.[22] In the same sense, the IF regimen promotes fat loss, a higher content of hypothalamic norepinephrine, accompanied by the expression of the neuropeptide Y gene in obese male mice.[23] Another study evaluated rats for 24 weeks with an ADF regimen, resulting in a decrease in fasting glucose and insulin, heart rate, and blood pressure,[24] in addition to a reduction in body weight and an increase in plasma corticosterone levels which is related to insulin sensitivity, also showed a significant decrease in heart rate and blood pressure in rats with ADF regimen for 16 weeks.[25]

Effect of fasting on aging

Aging is a multifactorial process that involves complex interactions between biological and molecular mechanisms linked to various factors such as oxidative damage to proteins, DNA, and lipids, inflammation, which lead to cellular dysfunction, and organ failure in organisms.[26] Recently it has been shown that aging is associated with metabolic dysregulation; through metabolomics, central metabolites have been identified in humans such as nicotinamide dinucleotide-adenine dinucleotide (NAD^+), nicotinamide-adenine dinucleotide phosphate (NADPH), α -ketoglutarate and β-hydroxybutyrate, which may mediate aging-related loss of metabolic homeostasis.[27] NAD^+, in addition to its function as a coenzyme for redox reactions, serves as a coenzyme for three enzymes involved in aging, such as sirtuins (SIRT), poly (ADP-ribose) polymerase (PARP), and cyclic ADP-ribose synthases. Substrates for sirtuins range from acetylated histones to transcription factors. The increase in sirtuin expression (SIRT-1) prolongs the lifespan of various organisms, including mammals.[28] After withdrawal, SIRT-1 triggers lipolysis and fat loss in adipocytes by repressing genes controlled by the fat regulator PPAR-γ.[29] In addition, SIRT1 activates the PPAR-α receptor by activating genes that increase fatty acid oxidation.[30] For more than 15 years, it has been shown that intermittent fasting and caloric restriction can extend the health and lifespan of the nervous system, involving the activation of signaling pathways and metabolic pathways for the improvement of degenerative disorders present in aging.[31,32] Concerning intermittent fasting, Table 1 and Figure 1 summarize various studies showing the effect of fasting on aging and oxidative stress. A study in healthy individuals with an ADF regimen provided a decrease in blood insulin levels and a marginal increase in the expression of NAD^+ Sirtuin-dependent deacetylase 3 (SIRT-3).[33] While in another study with overweight adults with an AIRT regimen for four days, serum glucose decreased, and the expression of the SIRT-1 genes and the autophagy gene LC3A and mTOR increased.[34] Autophagy refers to lysosome-dependent intracellular degradation, which regulates cellular adaptation to nutrient and oxygen depletion, as well as oxidative stress.[35] Currently, it is considered a nexus of metabolic and proteostatic signaling that determines critical physiological decisions in the body. Autophagic function deteriorates with age and plays a vital role in longevity mediated by fasting or caloric restriction (defined as a 10-40% reduction in caloric intake).[36] Both are considered interventions to improve health, increase stress resistance, counteract aging, and increase longevity.[34,37]

Recently, in a study with older adults, improved cognitive function was shown after 36 months of IF[14]. In obese older adults, caloric restriction for one year promotes weight loss and improves overall health.[38] In overweight adult patients, it decreased fasting insulin level and body temperature selected longevity markers after caloric restriction for six months.[39] Likewise, in a study of patients aged 18-65 years who presented metabolic syndrome who had a caloric restriction diet for 12 weeks, they showed a decrease in weight, glucose, insulin, HOMA, and lipids.[40]

The decrease in insulin activates the proteins AMPK (AMP-activated protein kinase) and the forkhead box O1 (FoxO1) proteins (a subfamily of transcription factors that mediate the inhibitory action of the insulin) in mammals that stimulate the expression of genes involved in autophagy, including the SIRTs.[41] The Fox subfamily of transcription factors plays an important role in longevity, the cell cycle, apoptosis, glucose metabolism, and adaptation to fasting.[42] FoxO1/FoxO6 expression in the liver increases in response to fasting; FoxO6 activates gluconeogenesis through several enzymes and other molecules.[43] In the same context, at the molecular level, it has been shown that mTor, for its acronym in English "mammalian target of rapamycin", is linked to the detection of energy, nutrients, and insulin intracellularly, involved in the coordination of metabolism, cell growth, proliferation, apoptosis, and inflammation.[44]

Also, mTOR signaling influences longevity and aging. The inhibition of mTOR complex 1 (mTORC1), a heterotrimeric protein kinase, has increased life expectancy and stem cell function.[45] One study showed that the presence of the mTORC1 gene in mice aged

with a prolonged 24-hour fasting regimen correlates with liver aging and with defects in ketogenesis. In contrast, inhibition of the mTORC1 gene is necessary for the activation of PPARα (peroxisome proliferator-activated receptor-α), which activates ketogenesis genes, suggesting that mTORC1 inhibition could extend the life expectancy of various organisms.[46]

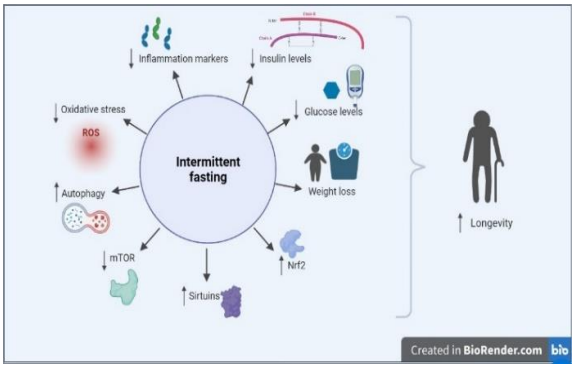

Figure 1. Summary of the effects of intermittent fasting on aging. [18, 20, 28,,33 45]

Table 1. Studies show the effect of intermittent fasting (IF) on aging factors and their relationship with oxidative stress.

Ref	Intervention groups	Effects of ADF on aging factors	
		Oxidative stress	Metabolic markers
53	C57BL/6J mice fasted for 24 hours.	Increases the expression of Nrf2-dependent genes that control the stress response. GPx4 expression increased, and GSH decreased. Significant reduction in MDA levels in skeletal muscle.	Not analyzed
40	Adults with metabolic syndrome had IF with and without caloric restriction for 12 weeks.	Not analyzed.	Decreases total cholesterol, triglycerides, LDL, glucose, insulin, $HbA1_C$, and HOMA.
18	Adults with a maximum fast of 13 days.	Increased total antioxidant capacity. Decrease MDA.	Decreases glucose, insulin, $HbA1_C$, cholesterol, LDL, and triglycerides.
14	Adults over 60 years of age with mild cognitive impairment (with ADF twice / week), with a 36-month follow-up.	Increases SOD activity decreases lipid peroxidation, C-reactive protein, and DNA damage.	Decreases body weight, LDL, triglycerides, total cholesterol, insulin, and glucose increase the HDL level.
15	Four young, healthy non-obese subjects with 58 hours of fasting.	Increased antioxidants, glutathione, $NADP^+$, and ATP levels.	The normal blood glucose level.
34	Eleven overweight adults during four days.	Increases the expression of the autophagy genes sirtuin-1 (SIRT1) and LC3A in the morning and BNDF in the night.	Decreases glucose and insulin. Increases expression of gene AKT2.
48	Fifty-seven subjects fasted for 15 days during Rahman. Thirty of them with the habit of fasting for 20 years.	Increases total serum antioxidant capacity. Decrease in the total oxidant state and the oxidative stress index.	Not analyzed.
17	Twenty-two overweight and obese women with IF for 24 hours, every other day for eight weeks.	Not analyzed	Increased apolipoprotein A4 and decreased apolipoprotein C2 and C3. Also a significant reduction in plasma triglycerides after the IF intervention.

33	Healthy subjects without obesity. Double crossover trial of 10 weeks, with two treatment periods with fasting of 21 days.	Sirtuin-3 (SIRT3) tended towards statistical significance.	Decrease insulin levels.
51	Ratas Sprague-Dawley with ADF during 24 months.	Decreases inflammation levels of oxidized glutathione, HNE, and carbonyl proteins. Increases the levels of reduced glutathione in the heart, protecting them against cardiac fibrosis.	Not analyzed
54	CD-1 mice with ADF for 11 months.	The level of GSSG in the cerebral cortex decreased, resulting in a significant increase in the GSH/GSSG ratio. Reduced levels of 4 HNE and nitrotyrosine in proteins in the cerebral cortex.	Not analyzed
16	Thirty-two obese subjects with high and low-fat diets and ADF during eight weeks.	No analyzed.	Decreased body weight, body fat, triglycerides, total cholesterol, and LDL. No change HDL Both diets were similarly effective.
52	Caloric restriction (CR) to varying degrees for five weeks and fasting (one week) in male Wistar rats.	CR 40-50%: Increases MDA, NOx, and decreases SOD. CR 20-30%: Increases ALT, AST and corticosterona. CR 60-70%: Increases SOD, GSH, and NOx. Fasting: Increases MDA, NOx, and decreases SOD and GSH.	Not analyzed
39	Subjects with overweight and caloric restriction for six months	Decreased DNA damage.	Decrease insulin level

AKT2 serine/threonine kinase; BNDF brain-derived neurotropic factor; CR caloric restriction; GSSG, glutathione disulfide; GSH, reduced glutathione; GPx4, glutathione peroxidase 4; HDL high-density lipoprotein; 4HNE, 4-hydroxy-2-nonenal; LDL low-density lipoprotein; MDA, Malondialdehyde; Nitrites NOx; SOD, superoxide dismutase

Effect of fasting on aging and its link with oxidative stress

Oxidative stress is defined as a pro/antioxidant imbalance detrimental to cells due to the excessive generation of reactive oxygen and nitrogen species.[47] For some years, the modulation of oxidative stress and damage markers in response to ADF and caloric restriction has been evidenced. A human study by Karsen *et al*. (2019) evaluated subjects with a regimen of a prolonged 15-day fast, which presented a higher total antioxidant capacity and a lower oxidative stress index than the non-fasting group.[48] Similarly, adults older than 60 years with regular IF for 36 months had a decrease in MDA, C-reactive protein, and DNA damage, accompanied by improved cognitive function.[14] Likewise, in another study with adults fasting for a maximum of 13 days, an increase in total antioxidant capacity, $ABTS^{\bullet+}$ radical scavenging capacity, at the same time, fasting reduces the level of TBARS and improves several metabolic indicators previously described.[18] Ketogenic diets have been linked to improved mitochondrial function and decreased oxidative stress. It has been shown that β-hydroxybutyrate reduces reactive oxygen species generation, improves mitochondrial respiration, activates nuclear erythroid-derived factor 2 (Nrf2), and modulates the NAD^+/NADH ratio. In addition, the ketogenic diet performs anti-inflammatory activity by inhibiting the activation of the nuclear factor NF-κB.[49] Nrf2 can be activated by various oxidative stressors, including caloric restriction and intermittent fasting.[50]

Sprague Dawley rats with an ADF regimen for two years inhibited the activation of NF-κB and pro-inflammatory proteins (IL-1β, TNF-α, IL-6) and decreased protein carbonylation. Moreover, increased glutathione protects age-related myocardial fibrosclerosis.[51] The duration of fasting is important; a previous study showed that fasting for one week in rats decreases antioxidant activity and increases oxidative damage in rat hepatocytes. While moderate caloric restriction increased antioxidant capacity in hepatocytes reflected an increase in glutathione (GSH) and superoxide dismutase activity (SOD).[52] Another recent study shows an increase in the expression of glutathione peroxidase-4, an antioxidant enzyme, and a reduction in malondialdehyde, a marker of lipid peroxidation in skeletal mice after a 24-hour fast.[53] Various studies in animal models show evidence that intermittent fasting and caloric restriction can delay aging by improving oxidative stress and preserving memory. In the same sense, in CD1 mice with ADF for 11 months, the concentration of 4-hydroxy-2-nonenal (4HNE) and nitrotyrosine in proteins in the cerebral cortex decreased indicators of oxidative stress. These changes accompanied better learning and memory in animals.[54] They highlight that rodents' age-related decline in learning and memory is associated with increased oxidative stress in the brain.[55]

CONCLUSION

It is currently recognized that IF has various beneficial effects on humans, caused by the regulation of energy metabolism or the improvement of oxidative stress and damage. IF has shown to improve metabolic biomarkers such as insulin and glucose, promote autophagy, and decrease obesity. In addition, IF reduces the appearance of the most frequent diseases that develop during aging linked to oxidative damage in proteins, DNA, and lipids, as well as inflammation. IF represents a non-pharmacological alternative to improve health in the adult population. However, more studies are required in the population to evaluate the effects of therapy on diseases associated with aging.

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