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The potential impact of glycine supplementation on the process of aging

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The potential impact of glycine supplementation on the process of aging

Abstract

Aging is a multifactorial process characterized by the progressive loss of cellular integrity, metabolic flexibility, mitochondrial function, and the gradual accumulation of oxidative and inflammatory damage. These changes increase vulnerability to age-related disorders, including cardiovascular disease, neurodegenerative conditions, metabolic syndrome, and frailty. Glycine, the simplest amino acid, has recently gained attention as a potential nutritional and therapeutic intervention to modulate various pathways implicated in aging. Beyond its structural role in collagen and other proteins, glycine is a critical precursor for glutathione- an essential intracellular antioxidant- plays a role in neurotransmission, and is involved in the synthesis of heme, creatine, and bile acids. Emerging studies suggest that glycine supplementation may alleviate oxidative stress, dampen chronic low-grade inflammation, improve insulin sensitivity, enhance mitochondrial function, and even mimic aspects of methionine restriction- a dietary approach known to extend lifespan in animal models. These combined effects may help preserve physiological function, slow the onset of age-associated diseases, and promote healthspan. Nevertheless, the evidence base is still evolving; most current data derive from animal models, in vitro experiments, and limited human trials. Rigorous, long-term, randomized controlled studies are needed to identify optimal dosing, determine long-term safety, and clarify whether glycine can be strategically leveraged as an anti-aging nutrient. If confirmed, glycine's safety, affordability, and accessibility may make it a compelling option for improving the quality of aging worldwide.

Keywords: glycine, aging, longevity, oxidative stress, inflammation, mitochondria, glutathione, metabolic health, safety, bioavailability

Introduction

Aging is a universal biological phenomenon that results in progressive functional declines, reduced adaptability, and increased susceptibility to chronic diseases [1,2]. It arises from complex interactions of genetic, environmental, and lifestyle factors that collectively affect cellular maintenance and repair systems. Key molecular hallmarks of aging include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, dysregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered

intercellular communication [3]. These processes lead to compromised organ function and the manifestation of age-related pathologies- cardiovascular diseases, type 2 diabetes, neurodegenerative disorders, osteoarthritis, and various cancers.

Nutritional interventions represent a promising avenue for mitigating aspects of aging and extending healthspan. Among them, amino acids- beyond their role as building blocks of proteins—serve as signaling molecules, precursors to critical metabolites, and regulators of metabolic pathways linked to longevity. Glycine, notable for its simplicity and versatility, stands out due to its involvement in multiple biochemical and physiological processes essential for maintaining cellular homeostasis [4,5]. Emerging research highlights glycine's potential to influence aging pathways through modulation of oxidative stress, inflammation, mitochondrial function, insulin sensitivity, and amino acid balance-mfactors intimately connected to both lifespan and healthspan [6, 7, 8, 9, 10, 11].

This review integrates current knowledge on glycine's roles relevant to aging, drawing from animal studies, mechanistic research, and early clinical evidence. We discuss how glycine may impact oxidative stress, inflammation, mitochondrial performance, metabolic health, and pathways influenced by amino acid balance. By exploring these mechanisms, we aim to provide a framework for future research and clinical trials, ultimately determining whether glycine could become a pragmatic strategy for promoting healthy aging in diverse populations.

Glycine and Oxidative Stress in Aging

Oxidative stress, a condition where the generation of reactive oxygen species (ROS) surpasses the capacity of antioxidant defenses, is recognized as a fundamental contributor to aging and many age-related diseases [1,2,12]. Excess ROS damage lipids, proteins, and nucleic acids, leading to molecular dysfunction, cellular senescence, and tissue degeneration. Aging organisms typically exhibit declining levels of endogenous antioxidants, such as glutathione, and diminished activity of antioxidant enzymes, including superoxide dismutase and catalase.

Glycine plays a central role in antioxidant defense by serving as a substrate for glutathione synthesis. Glutathione is a tripeptide (comprising glutamate, cysteine, and glycine) that detoxifies ROS, repairs oxidative damage, and maintains redox homeostasis [8,10,13]. Studies show that aging is associated with reduced intracellular glutathione, contributing to heightened oxidative stress and functional decline [14,15]. Supplementing with glycine, either alone or in combination with N-acetylcysteine (GlyNAC), has been shown in older adults to restore glutathione levels, lower oxidative markers, and improve mitochondrial function [11,16,17,18]. In rodent models, glycine supplementation helps maintain intracellular glutathione pools, mitigate protein carbonylation, and preserve mitochondrial DNA integrity—hallmarks of improved cellular resilience against oxidative damage [19,20,21].

By bolstering the antioxidant network and attenuating oxidative damage, glycine may help stabilize cellular function, preserve tissue architecture, and slow the progression of aging phenotypes. Future research should aim to identify optimal doses, durations, and combinations of glycine with other nutrients or lifestyle interventions to maximize its antioxidant benefits.

Inflammation, Immune Function, and Glycine

Chronic low-grade inflammation, often termed "inflammaging," is a pervasive characteristic of the aging process [1,22]. This inflammatory milieu stems from multiple sources: accumulating senescent cells that secrete pro-inflammatory cytokines, dysbiosis in the gut microbiome, impaired immune surveillance, and metabolic stress. Persistent inflammation not only accelerates tissue damage but also contributes to the onset and progression of age-related diseases such as atherosclerosis, sarcopenia, frailty, and neurodegenerative disorders.

Glycine has demonstrated anti-inflammatory properties across various models [23,24]. Experimental evidence suggests that glycine can inhibit the activation of NF-κB- a key transcription factor driving pro-inflammatory cytokine expression- thereby reducing the secretion of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and other mediators of chronic inflammation [25,26,27,28]. In animal studies, dietary glycine attenuates systemic inflammation caused by endotoxins or high-fat diets, improving survival and metabolic outcomes [25,29]. Glycine may also modulate macrophage polarization, promoting an anti-inflammatory M2 phenotype, and help maintain gut barrier integrity, reducing the translocation of endotoxins from the gut lumen into circulation [30,31].

If glycine's anti-inflammatory actions hold true in long-term human studies, supplementation may help alleviate the inflammatory burden that accelerates aging. By mitigating inflammaging, glycine could indirectly support healthier immune function, better muscle maintenance, and improved metabolic outcomes- translating to enhanced vitality and resilience in older populations.

Mitochondrial Health and Bioenergetics

Mitochondria are central hubs of energy production, cellular signaling, and metabolic regulation. With aging, mitochondria become less efficient, accumulate damage, and produce more ROS, perpetuating a cycle of declining function and increased oxidative stress [3,32,33]. Interventions that preserve mitochondrial integrity and functionality may slow the aging process and reduce the incidence of age-related diseases.

Glycine contributes to mitochondrial health in several ways. It is required for the synthesis of heme, a critical component of cytochromes involved in the electron transport chain. Adequate glycine levels support proper electron transport, reducing the electron leak that generates ROS [27,34]. Studies have found that glycine supplementation can improve mitochondrial protein quality control, enhance ATP production, and mitigate mitochondrial DNA damage in experimental models [28,30,35,36,37]. By maintaining a more efficient oxidative phosphorylation, cells can sustain better energy supply, maintain redox balance, and resist functional decline.

Additionally, glycine may influence mitochondrial biogenesis and autophagy, crucial processes for the replacement of damaged mitochondria with healthy ones [36,38]. Although human data remain sparse, these findings offer a strong biological rationale for glycine's potential to preserve mitochondrial function, a cornerstone of healthy aging.

Glycine, Metabolic Health, and Insulin Sensitivity

Metabolic dysregulation is a hallmark of aging, manifesting as insulin resistance, central adiposity, and impaired lipid handling [1,32,39]. Such changes predispose individuals to type 2 diabetes, cardiovascular disease, and diminished physical performance. Nutrient interventions that improve insulin sensitivity, enhance glucose uptake, and normalize lipid metabolism may thus slow metabolic aging and improve healthspan.

Glycine has emerged as a potential modulator of metabolic health. Animal and human studies suggest that glycine supplementation can improve insulin sensitivity, reduce circulating free fatty acids, lower triglycerides, and improve glucose tolerance [12,13,14,18,40]. Glycine may enhance adiponectin levels—an adipokine associated with improved insulin action—and modulate hepatic lipid metabolism, reducing the risk of nonalcoholic fatty liver disease [35,36,40,41,]. By ameliorating metabolic stress, glycine could help prevent or delay the onset of metabolic syndrome, a cluster of risk factors that become more prevalent with advancing age.

Restoring metabolic flexibility may also support skeletal muscle health, protect against sarcopenia, and maintain cognitive function—parameters strongly linked to well-being in older adults. Large-scale human trials are warranted to confirm whether sustained glycine supplementation can reliably improve metabolic endpoints and translate into tangible clinical benefits for aging populations.

Methionine Restriction, Glycine Balance, and Longevity

Methionine restriction, reducing dietary intake of the sulfur-containing amino acid methionine, is one of the most robust dietary interventions that extend lifespan and delay age-related diseases in several animal models [16,17,38]. By altering methionine metabolism, these interventions improve redox balance, modulate mTOR signaling, and enhance stress resistance. Intriguingly, glycine supplementation has been shown to partially replicate certain metabolic shifts seen with methionine restriction, potentially by balancing methylation reactions and supporting proper one-carbon metabolism [16,18,37].

This suggests that the ratio of glycine to methionine intake may be critical for optimizing metabolic health and extending lifespan. While direct evidence linking glycine supplementation alone to increased human longevity is limited, understanding how glycine interacts with dietary methionine and other nutrients could guide personalized dietary strategies aimed at healthy aging [42]. Further mechanistic studies and controlled feeding trials are needed to determine whether modulating the glycine-methionine axis can produce clinically meaningful enhancements in lifespan and healthspan.

Safety and Bioavailability

From a safety perspective, glycine is generally well-tolerated, with a long history of dietary exposure as it is abundant in collagen-rich foods (e.g., gelatin, bone broth) and commonly consumed at lower doses in regular diets [9,15,39]. Clinical trials using glycine or GlyNAC have reported minimal adverse effects, even with doses up to 15 g/day [11,16,43]. Glycine's small molecular size and neutral characteristics promote its rapid intestinal absorption and distribution to tissues. Its endogenous production and dietary presence also minimize the risk of toxicity compared to synthetic pharmacological agents.

Nevertheless, large, long-term human studies in older adults are required to confirm its safety over extended periods. Researchers must also consider potential interactions with medications (e.g., diabetes drugs, antihypertensives), as improving metabolic parameters may necessitate adjustments in drug regimens. Such evaluations will ensure that glycine supplementation strategies are not only effective but also safe for widespread application.

Current Limitations and Future Directions

While the theoretical framework and preliminary data supporting glycine's role in mitigating aging-related changes are compelling, several limitations constrain our current understanding. Much of the evidence is derived from preclinical models—rodents, cell culture systems, or short-term human pilot studies with limited sample sizes [10,11,20,21]. Standardized dosing regimens, participant stratification (e.g., by age, baseline health, genetic factors), and more sensitive biomarkers of aging are lacking in the current literature.

Future research should prioritize well-designed, randomized, controlled trials in diverse human populations. Incorporating biomarkers of cellular aging, such as epigenetic clocks, proteomic or metabolomic signatures, and functional outcomes relevant to daily living and longevity (e.g., muscle strength, cognitive performance, cardiovascular fitness), will provide more direct evidence of glycine's impact on aging trajectories [40,44,45,46]. Comparative studies examining interactions with other dietary interventions—such as calorie restriction, intermittent fasting, or supplementation with other amino acids—could help identify synergistic strategies.

Additionally, mechanistic explorations using modern omics technologies and CRISPR-based gene editing in model organisms may clarify how glycine influences signaling pathways relevant to aging. Such approaches will help establish whether glycine's anti-aging effects can be generalized or if they depend on individual metabolic phenotypes.

Conclusions

Glycine's multifaceted roles in antioxidant defense, anti-inflammatory modulation, mitochondrial maintenance, and metabolic regulation position it as a promising candidate for

promoting healthier aging. While definitive human studies linking glycine supplementation to slowed aging or extended lifespan remain sparse, the converging lines of evidence from animal research, mechanistic studies, and emerging clinical trials suggest substantial potential.

If ongoing and future investigations confirm glycine's benefits, this simple amino acid could become an integral component of nutritional strategies aimed at preserving function, delaying disease onset, and improving the quality of life in older individuals. Given glycine's accessibility, affordability, and safety profile, its integration into broader public health recommendations and personalized dietary interventions may represent a cost-effective and widely implementable tool in the pursuit of healthier, more resilient aging.

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