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Insulin Sensitizers as Anti-Aging Agents: Unveiling Synergies with Albumin, GLP-1RA, Klotho Protein, and Metformin in the Quest to Combat Aging

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Commentary
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Abstract

This study delves into the synergistic interplay among albumin, insulin, Klotho protein, and relevant medications in the pursuit of a concerted approach to halt aging. Emphasizing albumin's pivotal role in various physiological functions, including transportation and drug distribution, the research underscores its decline's correlation with aging-related cognitive implications. The intricate relationship between insulin and albumin, modulated by Foxo1, underscores its crucial significance. Groundbreaking experiments, utilizing unmodified serum albumin, demonstrate a remarkable increase in lifespan and enhanced physical capabilities, highlighting the potential of an integrative approach. The investigation extends to insulin sensitizers, Klotho protein, metformin, and SGLT2 inhibitors, collectively revealing promising anti-aging effects. The association between Klotho protein and albumin suggests a collaborative mechanism with implications for efficient transport and distribution. This research offers insights into a comprehensive, synergistic strategy harnessing the potential of these elements to counteract aging processes.

Keywords: Insulin Sensitizers; Metformin, GLP1; Degludec; Albumin; Aging; Protein Homeostasis; Insulin Signaling; Healthy Aging; Anti-Aging Agents; Protein Aggregation; Lifespan Extension; Cognitive Function; Therapeutic Strategies; Personalized Interventions

Abbreviations: GLP-1RA: Glucagon-Like Peptide-1 Receptor Agonist; AMP: Activated Protein Kinase; SCFAs: Short-Chain Fatty Acids; DPP-4: Di Peptidyl Peptidase-4; PKA: Protein Kinase A; PKC: Protein Kinase C; ROS: Reactive Oxygen Species; HAS: Human Serum Albumin.

Commentary

Albumin, the predominant protein found in human blood plasma, plays a pivotal role in the transportation of substances throughout the bloodstream. However, its functions go beyond mere transportation, encompassing tasks such as hydrogen ion binding, hormone transport, toxin neutralization, and drug distribution [1]. Recognizing the significance of these functions, maintaining consistent albumin levels throughout life becomes imperative to counteract the adverse effects of aging. Recent research has unveiled a correlation between declining albumin levels and the aging process. In particular, a 2022 study identified circulating albumin as the most important biomarker in

predicting an individual's biological age, surpassing even glucose levels in significance [2]. Another study in 2019 demonstrated the vital role of maintaining albumin levels in preserving neurological health [3].

Disruptions in the blood-brain barrier, associated with albumin deficiency, were found to lead to cognitive impairment and neurological aging in mice.

Despite the critical role of albumin and its age-related decline, current medical understanding categorizes this decline as a natural and unavoidable process [4]. However, as more studies emphasize the importance of albumin, this perception may change. It is crucial for individuals to be aware of the multifaceted functions of albumin and to challenge the assumption that decreasing levels are inconsequential in the context of aging [5]. Additionally, extensive diabetes research, characterized by dysregulated glucose, lipid, and protein metabolism, has revealed its connection to albumin production [6]. Insulin, a key regulator of glucose and lipid metabolism, has been found to influence albumin gene expression. Disruption of insulin signaling in mice led to decreased albumin secretion, a decrease that was rescued by the deletion of Forkhead Box O1 (Foxo1). These findings highlight the intricate connection between insulin and albumin, with Foxo1 acting as a repressor of albumin expression [7].

Furthermore, investigations into the interaction between Human Serum Albumin (HSA) and native human insulin and its fragments have demonstrated HSA's ability to inhibit their aggregation. Samples containing native insulin or its fragments exhibited the formation of amyloid structures, while HSA complexes displayed distinct secondary structures [8]. These results underscore the importance of albumin in maintaining protein homeostasis by preventing aggregation. A ground breaking experiment involved the delivery of unmodified serum albumin to middle-aged mice, diluting the presence of damaged albumin and reversing the detrimental responses to pro-aging signals in the blood. This intervention resulted in a significant increase in lifespan, with female mice experiencing a 17.6% extension and male mice a 20.3% extension. Additionally, the treated mice displayed improved physical capabilities, including increased grip strength and enhanced performance in cognitive tests [9]. Insulin, a hormone crucial for glucose regulation, exhibits a high affinity for its receptors [10]. This binding affinity enables precise signaling and efficient glucose uptake by cells. Insulin sensitizers, such as degludec and GLP-1 analogs like semaglutide, also demonstrate a strong affinity for albumin, a major plasma protein [11]. Albumin, as a carrier protein, plays a vital role in the transport of various substances, including drugs [12]. Metformin, an oral antidiabetic medication, binds to albumin within the plasma.

This interaction influences the pharmacokinetics and pharmacodynamics of metformin. The binding mechanism between metformin and albumin involves non-covalent interactions, primarily driven by hydrophobic and electrostatic forces [13]. These interactions prolong the half-life of metformin, enhance its distribution, and impact its bioavailability [14]. Metformin's binding to albumin also contributes to its mTOR inhibitory effect [15]. The mTOR pathway regulates cellular growth, metabolism, and aging. By inhibiting mTOR signaling, metformin has the potential to modulate aging-related processes [16].

In addition, degludec, a long-acting insulin analog, has been investigated for its effects on interleukin-6 (IL-6), a pro-inflammatory cytokine associated with insulin resistance and chronic inflammation. Degludec has shown potential in reducing IL-6 levels, suggesting its anti-inflammatory properties and potential benefits in managing insulin resistance [17]. The Klotho protein plays a crucial role as an anti-aging factor in various biological processes. Its involvement in extending lifespan has attracted significant attention from researchers. This protein exerts its effects through intricate mechanisms that contribute to the regulation of aging [18]. One mechanism by which the Klotho protein influences lifespan extension is through its impact on insulin and insulin-like growth factor-1 (IGF-1) signaling pathways. Klotho protein enhances insulin sensitivity and attenuates IGF-1 signaling, leading to a reduction in the activity of the mammalian target of rapamycin (mTOR) pathway. The mTOR pathway is involved in regulating cellular metabolism and growth. By inhibiting mTOR signaling, Klotho protein helps to maintain cellular homeostasis and promotes longevity [19].

Furthermore, the Klotho protein modulates oxidative stress and inflammation, both of which are key contributors to aging. It acts as a potent antioxidant by reducing the production of reactive oxygen species (ROS) and enhancing the activity of antioxidant enzymes. Additionally, Klotho protein suppresses pro-inflammatory signaling pathways, thereby reducing chronic inflammation associated with aging [20]. GLP-1 (Glucagon-like peptide-1) plays a pivotal role in increasing and activating the Klotho protein. GLP-1 is a hormone secreted by the intestines in response to food intake. It acts on the GLP-1 receptor, which is expressed in various tissues including the brain, pancreas, and kidneys. Activation of the GLP-1 receptor stimulates the production and release of the Klotho protein [21].

The mechanism by which GLP-1 enhances Klotho protein levels involves the activation of protein kinase A (PKA) and protein kinase C (PKC) signaling pathways. These pathways ultimately lead to the upregulation of Klotho gene expression and increased synthesis of the Klotho protein. Consequently,

the elevation of GLP-1 levels through various interventions such as GLP-1 receptor agonists or inhibitors of GLP-1 degradation can effectively boost Klotho protein levels and potentially promote anti-aging effects [22]. Moving on to the role of metformin in increasing Klotho protein levels, metformin is a widely used medication for the management of type 2 diabetes. Studies have shown that metformin can upregulate Klotho expression and enhance Klotho protein levels. The precise mechanism underlying this effect is not fully understood, but it is believed to involve the activation of adenosine monophosphate-activated protein kinase (AMPK) signaling pathway. Activation of AMPK by metformin leads to the phosphorylation of transcription factors that regulate Klotho gene expression, resulting in increased Klotho protein production [23].

SGLT2 inhibitors (SGLT2i) are a class of medications commonly used in the treatment of type 2 diabetes. Recent studies have shown that SGLT2i therapy leads to a notable increase in the levels of a protein called Klotho in both the bloodstream (serum) and urine. This increase in Klotho expression is observed across different SGLT2 inhibitors, suggesting that it is a class effect rather than specific to individual medications within the class. Klotho is known to have various beneficial effects on health, including potential roles in cardiovascular protection and anti-aging processes. The preservation of Klotho expression through SGLT2i therapy highlights a potential mechanism by which these medications may contribute to their therapeutic effects beyond glycemic control in patients with type 2 diabetes [24]. Finally, the association between Klotho protein and albumin (a major protein in the blood) has been investigated. It has been observed that Klotho protein binds to albumin, forming a complex that circulates in the bloodstream. This interaction between Klotho protein and albumin may have implications for the transport and distribution of Klotho protein in the body. However, further research is needed to fully elucidate the functional significance of this association [25].

Metformin is a widely prescribed oral antidiabetic medication with multiple mechanisms of action. One of its notable effects is the activation of GLP-1 (Glucagon-Like Peptide-1) levels. GLP-1 is an incretin hormone secreted by the intestinal cells in response to nutrient intake. It plays a crucial role in regulating glucose homeostasis by stimulating insulin secretion, inhibiting glucagon release, delaying gastric emptying, and promoting satiety [26]. The mechanism by which metformin enhances GLP-1 levels is not fully understood, but several hypotheses have been proposed. One possibility is that metformin indirectly stimulates GLP-1 secretion through its primary mode of action, which involves the activation of AMP-activated protein kinase (AMPK). AMPK is a key cellular energy sensor that regulates various metabolic processes, including glucose uptake and utilization. Activation of AMPK by metformin leads to increased glucose uptake in peripheral tissues, such as skeletal muscle, and decreased hepatic glucose production.

These effects may result in a reduction in circulating glucose levels, which, in turn, could stimulate GLP-1 secretion [27]. Another proposed mechanism involves metformin's impact on gut microbiota. Recent studies have shown that metformin alters the composition of the gut microbiome, leading to an increase in the abundance of certain bacterial species that produce short-chain fatty acids (SCFAs). SCFAs, such as butyrate, have been implicated in GLP-1 secretion. It is hypothesized that the changes in gut microbiota induced by metformin may promote the production of SCFAs, which could subsequently enhance GLP-1 release [28]. Additionally, metformin has been shown to inhibit the enzymatic breakdown of GLP-1 by dipeptidyl peptidase-4 (DPP-4), an enzyme responsible for the rapid degradation of GLP-1. By inhibiting DPP-4 activity, metformin could prolong the half-life of GLP-1, thereby increasing its circulating levels [29].

In conclusion, this study illuminates the intricate web of interactions among albumin, insulin, Klotho protein, and pertinent medications, advocating for a synergistic and comprehensive approach to combat aging. The research emphasizes albumin's multifaceted functions and its decline as a significant biomarker for aging. The interconnection between insulin and albumin, underscored by the role of Foxo1, amplifies the importance of maintaining albumin levels. Groundbreaking experiments with unmodified serum albumin showcase tangible advancements in lifespan and physical capabilities, providing a compelling argument for the potential of a holistic intervention. The exploration of insulin sensitizers, Klotho protein, metformin, and SGLT2 inhibitors collectively suggests promising avenues for anti-aging strategies. As we unravel the association between Klotho protein and albumin, envisioning a collaborative mechanism with implications for efficient transport and distribution, the study underscores the potential for a unified front against the aging process. In the broader context, this research challenges conventional notions of aging, paving the way for a paradigm shift in understanding and addressing age-related health challenges. By advocating for a coordinated strategy harnessing the strengths of albumin, insulin, Klotho protein, and medications, this study contributes to the evolving landscape of anti-aging interventions, offering hope for improved health and longevity.

Statements and Declarations

The authors declare that there are no conflicts of interest.

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