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[Commentary] Insulin Sensitizers as Anti-Aging Agents: Exploring the Role of Albumin and its Implications for Healthy Aging

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Abstract

This manuscript delves into the potential of insulin sensitizers, specifically Metformin and GLP1 with Degludec, as anti-aging agents, focusing on the multifaceted functions of albumin and its association with age-related changes.

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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 research on diabetes, 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 groundbreaking 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]

In conclusion, the pivotal role of albumin in the aging process, along with its association with insulin signaling and protein

metabolism, highlights the potential of insulin sensitizers such as Metformin and GLP1 with Degludec as anti-aging agents. Further research is necessary to explore the underlying mechanisms governing the interaction between insulin, albumin, and aging, with the objective of developing interventions that effectively counteract age-related decline. Understanding the multifunctional capabilities of albumin and its modulation by insulin sensitizers may pave the way for innovative therapeutic strategies to promote healthy aging.

Statements and Declarations

The authors declare that there are no conflicts of interest.

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