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Review: The Role of Insulin in Aging: Mechanisms, Impact, and Therapeutic Perspectives

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دور الإنسولين في الشيخوخة: الآليات، التأثير، والمنظورات العلاجية

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ABSTRACT

Aging is characterized by the age-dependent decline of physiologic function that in turn raises susceptibility to death. This process of degeneration is characteristic for all forms of life and constitutes a major driving force behind many diseases including obesity, type 2 diabetes mellitus, Alzheimers disease and heart disease. Failures in insulin, an essential hormone, have been shown to be associated with most of the age-related diseases. Insulin is a critical hormone controlling metabolism, development, cell division and differentiation. It is regulated by two major mechanisms: release and clearance of insulin from the blood as well as sensitivity to a tissue's tissues. Aging disrupts these processes, which contributes to insulin dysfunction, and increases the incidence of disease and death. Insulin action in aging is the purpose of this project, and its contribution to age-related diseases. Also indicate that improving insulin function may be an effective way to promote healthier and longer life.

Keywords: Aging, Insulin, Insulin resistance, Obesity, Diabetes, Sarcopenia

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INTRODUCTION:

When we age, insulin is the major hormone that enables our cells to take up glucose from the bloodstream. Available evidence suggests calorie restriction results in increased life span[1]–[5]. Calorie-restricted diets can significantly extend the life spans of mammals, and lean animals are less prone to age-related diseases than their obese cousins. The mechanisms are still not yet fully explained though. The studies also find less chemical signaling among insulin-like hormones in fat cells when lifespan is extended. The study illustrates insulin's action on controlling its synthesis. Blocking the action of insulin in certain cells will help the body to live long and healthy for a longer period with aging. These effects are caused by a decrease in insulin-like signaling that is associated with extension of life span and that can be either mutations in the insulin-like receptor (InR) or the receptor substrate, or ablation of insulin producing cells [1], [2]. Insulin influences aging in a dual manner, because it is able to influence the aging processes itself independent of its production and directly intermediates in tissue-aging.

Second, low insulin levels are not only protective against infection and age-related diseases, but they promote cellular robustness and longevity [5],[6]. This relationship illustrates the integration of hormonal output, dietary intake and metabolic control within the elaborate physiological network that orchestrates aging. Aging is characterized as an incremental loss of function, leading to greater susceptibility to death. The decaying process is visible in everything that lives and is a major cause of most abnormal states of health -- including diabetes, obesity, neurodegenerative disease and heart failure. Changes and disorders of the insulin have been implicated in most age-associated diseases. Their receptors, in addition to other roles, transduce the actions of insulin and IGF1 on cellular proliferation, differentiation and metabolism as well as growth. Its effects are determined by the circulatory, secretory, clearance and tissue sensitivity of insulin. These processes are impaired with age and contribute to disrupted insulin action and an increased risk of mortality and morbidity. An interesting route to better health and a longer lifespan is improved insulin action [7]. The insulin sensitive target tissues are adipose tissue, liver and muscle; however, development of insulin resistance is an undesirable biological response. As increased release of glucose is thwarted by resistance to insulin, the body will compensate by creating more insulin and stimulating beta cells. Metabolic consequences of the insulin resistance may cause dyslipidemia, endothelial dysfunction, elevation in inflammation markers and high water retention sugar, blood pressure incompatible with life urine collections such as prothrombosis and central obesity. Recognition of the etiology and presentation of insulin resistance and the role of a multidisciplinary team have implications for its management and prognosis based on earlier studies [1], [4]-[8]. The data presented in the review also supports evidence that the cluster of features commonly referred to as metabolic syndrome, syndrome X or insulin resistance syndrome have a common etiology with hyperinsulinemia and insulin resistance. There is, of course, evidence to suggest that with increasing age people become more insulin-resistant and glucose-intolerant. Environmental (lifestyle) factors which have been suggested to contribute to this functional decline primarily are obesity, abnormal fat distribution and lack of physical activity in old age or low levels of physical activity with aging. Adjustable bad environmental or lifestyle factors are responsible for increased occurrence of these metabolic syndrome diseases that lead to hyperinsulinemia and high insulin levels. Reversal of these age-related detriments in these old animals improved insulin sensitivity and glucose tolerance.

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In contrast, insulin secretion may decline with age after adjustments for differences in adiposity, fat distribution and PA or exercise. Irrespective of improvements in life style and other environmental influences, they might contribute to the glucose intolerance observed among much older men [8]. It has been suggested that age-related elevations in glucose are associated with deranged insulin production, and there is sex-dimorphism in respect of the effect of aging on insulin resistance [9]. Investigation with the Intravenous Glucose Tolerance Test revealed that, in comparison to healthy young individuals and young patients with type 2 diabetes, insulin resistance is a characteristic feature of the common form of aging in elderly persons. Thus, senility has become an important or inevitable high risk factor of glucose metabolism disorder and metabolic syndrome including the latter's complications[10]. The insulin production and clearence, as well as the dialogue between insulin and target tissue, were altered in aged individuals. They are located between the healthy group and patients with type 2 diabetes, but especially older have susceptibility to a risk of impaired glucose tolerance/diabetes mellitus as well as its vascular complications.

Evolutionary Role of Insulin in Ageing Regulation

Among the most well-conserved biological processes is insulin signaling, essential for development, reproduction and energy balance. It was first demonstrated that it extends the lifespan of more primitive organisms like Caenorhabditis worms: Mutations in genes encoding for insulin-like signaling lead to a substantial increase in lifespan there. These studies also represented a paradigm shift, namely that insulin and related pathways became identified as a master regulators of aging (as well as mTOR signaling), in addition to being involved in the control of metabolism. Loss of daf-2 gene function can double C. elegans lifespan [11]. Daf-2 is a homolog of the insulin/IGF-1 receptor. This effect is mediated by the Caenorhabditis elegans ortholog of mammalian Forkhead box O (FOXO) transcription factor, dauer formation abnormal protein16 (DAF-16). In order to live longer, you need autophagy, detoxification and the activation of genes that protect against stress — all three are things over which DAF-16 ultimately presides. It has also been found that a higher longevity in Drosophila melanogaster is the result of mutation in the insulin receptor substrate CHICO or is attributed to decrease in insulin like peptides (dILPs) [12]. Other studies showed that long-lived mice with enhanced resistance to oxidative stress and survival had an overexpression of FOXO transcription factors or a partial deletion of the IGF-1 receptor [13], [14]. From an evolutionary biology perspective, these findings support what's called the "disposable soma theory" of ageing: that living things balance expending energy on reproduction with maintaining themselves. Dietary restriction leads to maintenance not only because of the reduced insulin signaling but also in the face of it, leading to resistance against stress and delay of aging. By contrast, in nutrient-rich conditions short-term growth and reproduction take precedence over long-term survival, which is ensured by insulin signaling. Curiously, studies on very old people have shown that humans have evolved in similar ways. Over-representation of specific FOXO3A polymorphisms is associated with longevity, which may indicate that genes controlled by FOXO have some kind of protective benefit [15].Those with Laron syndrome or naturally lower IGF-1 levels, for example, appear to age more slowly and have a reduced risk of cancer, even though they are significantly smaller than average.

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All of these findings from different animals lead to the same basic biological principle: reducing insulin/IGF-1 signaling, even a little, especially in maturity, increases healthspan and lifespan. Thanks to this new information, we may start working on anti-aging treatments that target pathways connected to insulin [16].

Insulin resistance:

When glucose is not efficiently used by the body, especially by the liver, muscles, and adipose tissue, a condition known as insulin resistance (IR) develops, which causes compensatory hyperinsulinemia to worsen with time. Obesity amplifies the symptoms of insulin resistance (IR) [17], which in turn increases the likelihood of developing prediabetes, diabetes, and cardiovascular disease. Hyperglycemia, hypertension, dyslipidaemia, and central adiposity are all risk factors for cardiometabolic atherothrombotic events, and they are all underpinned by IR [18],[19].The hyperinsulinemic euglycemic clamp method is considered the gold standard for determining insulin sensitivity [20]. You can estimate insulin resistance by taking your fasting glucose level (in mg/dL), multiplying it by your fasting insulin level (in µU/mL), and then dividing by a constant, with the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) being the most widely used method for this. Do this. Gerald Reaven of Stanford University expanded and improved upon the original idea of IR, which dates back to the time of Himsworth's description [21]. Clinical diagnostic criteria for metabolic syndrome now include it as the underlying metabolic disorder [22]. A broader definition was then suggested, including liver problems, high uric acid levels, and increased inflammation along with the original four measurable signs: central obesity, high blood pressure, high blood sugar, and abnormal cholesterol levels.

Clinicians should aggressively identify the illness and manage it with lifestyle and pharmacologic interventions, according to recent recommendations [23]. Advancement in age is a key risk factor for deteriorating IR, which is unchangeable. Several variables, including body fat, muscle mass, physical fitness, chronic disease, and medication usage, affect the linearity of the connection between aging and decreased insulin sensitivity [7]. The body's ability to use insulin, however, gradually and irreversibly decreases as we age. We still don't fully understand the cellular and signaling processes that cause insulin activity to vary with age.

The inflammatory condition, adipokine secretion, and location of adipose tissue are all impacted by aging, which also increases lipotoxicity. These fat alterations play a major role in the development of insulin resistance and type 2 diabetes (T2D) with age [24]. Sarcopenia is a natural part of becoming older, and it influences the secretion of growth-promoting myokines and neurochemicals that may make people less responsive to insulin. Increased weakness and lower ability to function are the outcomes of the harmful effects caused by these changes in muscle and fat [25].

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Biological Mechanisms Linking Insulin Resistance to Aging

1. Oxidative stress and mitochondrial dysfunction.

Insulin resistance can lead to oxidative stress in several ways, like disrupting how the body processes carbohydrates and fats, increasing the activity of GSK-3β, and affecting cell survival, energy balance, and how mitochondria work, are accompanied by reduced expression of pertinent molecules such as choline acetyltransferase and neurotrophins which is induced by brain IR [26]. Oxidative stress can be aggravated by factors like low oxygen and diminished blood flow, which cause more of the damaging substances to accumulate. Neurotoxicity associated with these reactive species may be due to the damage of cell membrane components, including lipids, proteins and DNA [27], [28]. It is noteworthy that defective mitochondria are linked to neurodegeneration in AD [29], [30]. Oxidative injury marks the onset of neurodegeneration. Oxidative Stress When ROS and their antioxidant defenses are overwhelmed (or there is the inability of the body to remove them effectively) oxidative stress ensues [31]. Not only are mitochondria involved in energy and free radical production, they also play a critical role in the prevention of neurodegenerative diseases and aging. Reactive oxygen species (ROS) have been demonstrated with respect to the brain regions of AD patients and during animal experiments, within which cerebral mitochondria is one of primary sources of ROS [32], The oxidative imbalance might be a central in the pathogenesis of Alzheimer's disease (AD) and based on that fact indeed, as a result from malfunctioning mitochondria Produce less ATP but excessive amount of reactive oxygen Species (ROS) [32].

Brains affected by Alzheimer's disease show a decline in enzymes that play an essential role in metabolic processes such as glycolysis, the Krebs cycle, and the respiratory chain. When glucose metabolism is impaired, it leads to less ATP production, problems with nerve function, loss of connections between nerve cells, and damage to the brain [32],[33]. It is important to mention that higher activity of mitochondrial enzymes and oxidative stress are signs of the early stage of Alzheimer's disease, happening before amyloid plaques can be seen in animal models of the disease [34]. The exact relationship between Aβ oligomers, mitochondrial activity, and ROS generation is still unclear because previous studies have shown contradictory results [35]; therefore, further study is needed to determine what elements start it all.

2. Chronic inflammation ("inflammaging").

Inflammaging is defined as the age-related rise in chronic, low-grade inflammation that does not manifest as an illness [36]. These indicators of inflammation, which include C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and interleukin 1 beta (IL1beta), are powerful risk factors for several age-related illnesses and death. Researchers believe that some of these circulatory variables are made locally and then seep into the bloodstream. The condition of inflammaging is contributed to by several causes, including cellular debris and organelle component buildup, senescent cell accumulation, immunosenescence, gut microbiome alterations, and coagulation system dysregulation. There is a constant cycle of damage and healing involving macromolecules, cells, and tissues. Regular tissue remodeling includes chronic

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inflammation, which aids in tissue repair and turnover. On the other hand, tissue deterioration due to active leukocytes, cytokines, or collagen deposition might result from a chronic inflammatory response [37]. The hypothalamus is a prominent brain region in which associations between inflammation and aging are being suggested.

An inflammatory response is crucial to the development and advancement of Alzheimer's disease. The buildup of Aβ, which causes continuously activated glial cells to produce inflammatory chemicals, is fundamental to the neuroinflammation theory of Alzheimer's disease [38]. Higher amounts of inflammatory proteins like IL-1, IL-6, TNF-α, and TGF-β are often found in the cerebrospinal fluid of people with Alzheimer's disease [39]. The mechanism of activation of microglia and astrocytes, as well as the release of substances which are inflammatory and potentially toxic (i.e. “neuroinflammation”) has been used to described in the literature [40]. Upon activation, microglial cells—primary immune cells of the brain—signal central inflammation and could be an origin of brain pathology [41]. Studies have shown that neuroinflammation considerably accelerates brain cell damage, which is observed in Alzheimer’s disease and results in nerve cell harm, increased oxidative stress, and decreased communication between cells. This is the case for multiple neurodegenerative diseases []. The AR participation in maintaining neuroinflammation is complicated by the fact that IR also plays a role. Peripheral IR may influence neurodegeneration and consequently the pathogenesis of AD [43]. Glucose interaction transforms proteins and lipids into advanced glycation end products (AGEs) [44]. This resistance increases the expression of IDE and promotes the production of AGEs. Specifically, high AGE are found in IR patients [45]. AMY and NFTs, the hallmark formations of AD, are themselves reservoirs of toxic AGEs. AGEs can also cause brain vascular diseases apart from RAGE receptor activation [46]. RAGE mediates effects of AGEs and Aβ to stimulate inflammation, with consequences for both the brain's vasculature and neurodegeneration. Its level of expression is also higher in subjects with AD and T2DM [47]. To further link inflammation and IR, it has been shown that macrophages, key players of the neuroinflammatory terrain, release inflammatory molecules with an impact on insulin signaling.

[48].Although insulin has anti-inflammatory and neuronal protein-promoting properties, its signaling in the brain is impacted by several variables, including apoE-ε4, which contributes to the advancement of Alzheimer's disease [49].

The Role of Insulin in the Brain:

Research on animals shows that insulin receptors are found in different parts of the brain, like the hippocampus, cerebral cortex, and cerebellum, and while all brain cells have these receptors, the amount varies. Although similar receptors are found in human brains [50],[51], changes in the central nervous system's insulin signaling may accelerate brain ageing, affect plasticity, and cause neurodegeneration [52].
The insulin receptor and the IGF-1 receptor (IGF-1R), which are widely distributed throughout the brain, are involved in the interaction between insulin and insulin-like growth factor 1 (IGF-1) [53]. Several brain areas, including the hypothalamus, olfactory bulb, and hippocampus, are highly expressed with insulin receptors, according to animal studies. On the flip side, the

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thalamus, neocortex, and hippocampi are where IGF-1R is most highly expressed in mouse brains [54],[55]. In the brain, these receptors can work together to improve signaling [56]. A further in-depth analysis of insulin receptor categorization identifies two main isoforms: IR-A, found mostly in adult neurons, and IR-B, found mostly in fat, liver, and muscles [57]. Remarkably, insulin receptors are present in both neuronal and glial cells, and both IGF-1 and IGF-2 may bind to them [58]. When the combination of alpha and beta subunits known as insulin tyrosine kinase receptors binds to insulin, the complex of events known as insulin signaling is triggered [59]. The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway is essential for metabolism, making proteins, and keeping cells alive, and it gets activated when insulin binds to its receptors. Besides being responsible for mitochondrial activity, this pathway is related to DNA replication and protein synthesis [60], [61]. Through binding to the growth factor receptor-bound protein-2 (Grb-2), a second major signaling pathway—mitogen activated protein kinase (MAPK)—is triggered. Cell cycle and glucose metabolism are only two of several processes affected by this route, which controls the function of numerous proteins and transcription factors [62].

Sarcopenia increases the risk of insulin resistance in aging skeletal muscle:

There is an associated relationship between skeletal muscle mass and insulin sensitivity that has implications for the regulation of energy and glucose homoeostasis [63]. Glucose uptake by skeletal muscle and insulin sensitivity are both increased with the higher proportions of muscle mass, as suggested by studies [64]. Skeletal muscle insulin sensitivity may also be reduced as a result of sarcopenia, which is when muscle mass and strength decline. In this procedure, myostatin is crucial. Myostatin inhibitor treatment ameliorated sarcopenia and enhanced insulin sensitivity in skeletal muscles of old mice after 4 weeks of treatment [65]. Insulin sensitivity and skeletal muscle glucose utilization are both enhanced in myostatin deficient mice [66]. Thus, insulin resistance in aged skeletal muscle can be exacerbated by sarcopenia, which is characterized by a loss in both muscle mass and strength.

Epidemiological findings on insulin and aging:

Epidemiological studies in humans indicate that insulin has an anti-aging effect. Although insulin resistance tends to rise with age, normal glucose tolerance, low fasting insulin levels, and increased insulin sensitivity are often maintained by centenarians in comparison to persons older than 75 years [67]-[69]. Fasting insulin concentrations are lower in shorter men, which may explain why they live longer [70]. Central adiposity is linked with an age-related rise in fasting insulin levels and insulin resistance in people with normal glucose tolerance [71],[72]. Researching the effects of hyperinsulinemia on health might also involve measuring circulation C-peptide concentrations and using meal frequency questionnaires to assess the insulinemic potential of the diet. A diet with a higher insulinemic potential was associated with a greater risk of dying from any cause, heart disease, and cancer, based on studies from the Nurses' Health Study and the Health Professionals Follow-up Study, which included nearly 2,800,000 years of data from participants [73]. Importantly, these correlations did not depend on body mass index.

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Therapeutic Measures and Future Prospects

Therapeutic Strategies

1. Lifestyle Interventions

Modifying someone's lifestyle is still essential to control insulin resistance at that person's particular age and also in developing conditions associated with it. Regular exercise and strict dieting, as well as reduced intake of saturated fats and carbohydrates, increase insulin sensitivity and decrease the low levels of chronic inflammation associated with aging. In addition, mitochondrial function is also improved while oxidative stress and metabolic health are saved [74].

2. Pharmacological Approaches

Managing hyperglycemia and insulin resistance remains the only pharmacologic treatment available for elderly patients. While metformin remains the most common medication used for older patients, some of them do require insulin therapy as beta-cell function declines. Newer clinical guidelines put greater focus on personalized insulin treatments for older adults due to the chances of hypoglycemia, cognitive decline, and functional difficulties. This population is now recommended to use CGM systems and advanced insulin delivery systems, like insulin pumps, to improve their glucose level control and management while minimizing the risk of complications [75].

3. Anti-Inflammatory Strategies

Researchers have looked into the effects of low-dose aspirin, statins, and omega-3 as well as omega-9 fatty acids to see if they can help reduce chronic inflammation and maybe improve insulin sensitivity in the central nervous system. Research indicates that delivering fatty acids directly to the central nervous system may help alleviate inflammation in the hypothalamus, thus re-establishing metabolic balance in animal studies. Engaging in exercise is a solid method for reducing inflammation, helping insulin perform better both systemically and in brain functions [76].

Innovative and Emerging Therapies

1. Novel Insulin Analogues

Basal insulin analogs administrated once a week have made important progress. The objective of those sustained-release preparations is to relieve part of the burden that patients, particularly in the elderly, assume by reducing the risk of serious side effects such as hypoglycemia and forgotten doses. Both adherence and safety stand to gain. Something enormous has changed. Recent findings suggest that the analogues may have therapeutic potential. Example: in phase 3 trials [77], once-weekly insulin icodec as basal insulin appears to have a comparable safety profile with

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daily insulin glargine (in terms of hypoglycaemia rates) and to be as effective as the latter in reducing HbA1c. Particularly in the elderly, they may help to change the game of diabetes management by reducing daily routine complexity and ease adherence.

2. Beta-Cell Replacement Therapies

Some very fascinating possibilities are opening up as a result of recent advances in regenerative medicine. Animal studies and preliminary human trials with encapsulated pancreatic islet cells, either from pigs or human stem cells, have yielded encouraging results. Potentially requiring little immunosuppressive medication, these methods may help the body produce insulin autonomously for a long period [78].

3. Modulating Insulin/IGF-1 and mTOR Pathways

Animal research and genetic analyses point to a potential anti-aging effect of mTOR and insulin/insulin-like growth factor (IGF-1) pathway targeting. The best strategy to slow metabolic decline with age without affecting other bodily processes is the subject of active research into tissue-specific manipulation of these pathways. Delaying the onset of age-related diseases has been demonstrated by reduced insulin/IGF-1 signaling, and recent reviews and experimental studies confirm that inhibiting the mTOR pathway, either genetically or with pharmacological agents like rapamycin, increases lifespan in many organisms, including mice.To maximize health advantages while minimizing negative systemic effects, researchers are currently investigating strategies to selectively modulate these pathways in certain organs (such as adipose tissue, liver, or brain) [79].

4. Targeting Hypothalamic Microglia

Age-related insulin resistance in the brain is partly driven by microglial inflammation in the hypothalamus. Future therapies may focus on reducing microglial hyperactivation as a novel approach to preserving central insulin sensitivity and supporting healthy aging [80].

Future Research Directions

- Personalized Medicine: Integration of genomic, metabolic, and phenotypic data to tailor therapeutic regimens based on the individual's risk profile and response.
- Further Development of Regenerative Solutions: Ongoing clinical trials on replacing beta cells with stem cells and using bioengineering methods could change how insulin dependence is managed in older people.
- Mechanistic Exploration: Greater understanding of tissue-specific insulin signaling and cross-talk is critical to develop precise anti-ageing metabolic interventions.
- Broader Clinical Use of Digital Health Tools: Widespread adoption of CGM and remote monitoring will continue to optimize glycemic control and quality of life for older adults.

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CONCLUSION:

Metabolic syndrome, obesity, diabetes, cardiovascular disease, learning and memory in the brain, age control, and many other human pathophysiological capabilities rely on insulin. Insulin resistance syndrome is characterized by low brain insulin concentrations, reduced insulin activity, and chronic peripheral insulin elevation. The pathophysiology of insulin and aging, in conjunction with risk factors and their related consequences, links all of these together. Aging makes the effects of oxidative stress and inflammation worse, but these are simply the cost of sustained high levels of insulin. Collectively, these occurrences may disrupt behaviors that lead to health and longevity. Derangements of insulin in the aged suffering from ARCD can be circumvented, ameliorated and/or attenuated by therapeutic modalities.

Conflict of interests.

The authors decelerates that there is no conflict of interest.

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الخلاصة

يُعرف الشيخوخة بأنها فقدان تدريجي للوظائف الفسيولوجية، مما يزيد من خطر الوفاة. هذا التدهور موجود في جميع أشكال الحياة ويعد مساهمًا رئيسيًا في العديد من الأمراض والمشكلات الصحية، مثل السمنة، ومرض السكري من النوع الثاني، ومرض الزهايمر، وأمراض القلب. وقد ارتبط انخفاض وظيفة الإنسولين، وهو هرمون حيوي، بمعظم الاضطرابات المرتبطة بالتقدم في العمر. يلعب الإنسولين دورًا أساسيًا في تنظيم الأيض والنمو وانقسام الخلايا وتمايزها. تتحكم وظيفته في آليتين رئيسيتين: إفرازه وإزالته من مجرى الدم، وحساسية الأنسجة المستهدفة له. يؤثر التقدم في العمر سلبًا على هذه الآليات، مما يؤدي إلى ضعف وظيفة الإنسولين وزيادة خطر الإصابة بالأمراض والوفاة .تهدف هذه الدراسة إلى دراسة تأثير الشيخوخة على وظيفة الإنسولين ودوره في تطور الأمراض المرتبطة بالعمر كما تشير إلى أن تعزيز وظيفة الإنسولين قد يمثل استراتيجية واعدة لتعزيز حياة أطول وأكثر صحة.

الكلمات المفتاحية : الشيخوخة , الانسولين , مقاومة الانسولين, السمنة , السكري , ساركوبينيا