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Pathophysiology of Insulin and Ageing with Concomitant Risk Variables and Sequelae

Chrysanthus Chukwuma SR*

*The Chrysanthus Centre for Future-Oriented Studies Abakaliki, Ebonyi State, Nigeria.

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ABSTRACT

Insulin has effects on ageing and lifespan, and provides a mechanism for gene manipulations for people to have prolonged and healthier lives and as preserved insulin sensitivity is associated with longevity. The insulin function is dependent on mechanisms which are determinants of its circulating abundance, secretion, clearance and sensitivity in its target tissues. Ageing enhances deranging impacts on these processes which debilitate insulin functionality, resulting in augmented risk for morbidity, untoward sequelae and mortality. Certain models of impaired insulin signaling are associated with prolonged longevity or resistance to life-threatening factors, such as oxidative stress. Insulin and insulin signaling are associated with successful ageing and longevity. Calorie restriction enhances lifespan in numerous species. Adequate control of factors associated with risks for obesity, diabetes, cardiovascular disease, and other insulin and ageing sequelae can be retarded in the elderly with optimum sustenance of their lifestyles.

Keywords: Obesity, Diabetes, Metabolic syndrome, CVD, Insulin resistance, Lifespan

INTRODUCTION

In the ageing process, the hormone, insulin is the pertinent substance that potentiates glucose uptake from the blood stream by cells. There is evidence that calorie restriction enhances longer lifespan [1-5]. Also, controlled famine [1,3] can considerably sustain mammalian lifespan; and lean mammals are less vulnerable to old age disorders as obese ones [1,4]. The mechanisms have not been clearly elucidated, though.

It was observed that chemical messages from an insulin-like hormone are decreased inside fat cells; whereupon lifespan is enhanced. The investigation also highlights the role of insulin in regulation of its synthesis [1,4]. The inhibition of insulin action within specific cells allows the entire body to maintain a prolonged health. Thus, ageing is retarded, if there is decrement in insulin-like signaling with resultant extension of life expectancy, if either the insulin-like receptor (InR) or its receptor substrate undergoes mutation, or there is ablation of insulin-producing cells [1]. Although, it is not definite when insulin affects ageing, insulin independently achieves this effect, regulates its own production, and directly regulates tissue ageing. Thus, low insulin concentrations promote stronger and healthier cells for the prevention of infections and age-related disorders [5,6].

THE REGULATION OF AGEING AND INSULIN PROCESSES

The regulation of ageing is an intricately complex physiological mechanism inculcating secretion of hormones, nutritional inputs, and regulation of metabolism. The characterization of ageing is intermittent dissipation of physiological functionality with resultant increment in susceptibility to mortality. The progressive debilitative process is evident and manifests in all biota, and constitutes the prime risk factor for aberrant disorders, such as obesity, diabetes, neurodegenerative and cardiovascular diseases.

A vast majority of age-related diseases have been linked with the derangement of insulin action. Insulin and IGF1 receptors mediate their effects inter alia on regulating cell proliferation, differentiation [7], metabolism and growth [6].

Corresponding author: Chrysanthus Chukwuma SR, The Chrysanthus Centre for Future Oriented Studies Abakaliki, Ebonyi State, Nigeria, Tel: +2349169698423; E-mail: cfos_nigeria@yahoo.com

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Insulin action is dependent on mechanisms which are determinants of its circulatory concentrations, secretion, clearance and sensitivity in target tissues. Ageing has debilitating impact on these mechanisms which derange insulin action leading to elevated risk in morbidity and mortality. The improvement of insulin action is a pertinent trajectory for healthier and longer life span [7] and expectancy.

INSULIN, AGEING, HYPERTENSION AND TYPE 2 DIABETES

It is established that ageing correlates with an elevated incidence of hypertension, type 2 diabetes, and coronary heart disease. Speculations are rife as to the underlying common process [8] in the etiology of these disorders as to manifest in syndemics [9], comorbidity [10], or frequent clustering of these disorders in the same person [8]. Epidemiological and clinical evidence depict that insulin resistance and/or hyperinsulinemia correlate with aberrations, such as glucose intolerance, dyslipidemia presenting as elevated plasma triglyceride and decreased high-density lipoprotein-cholesterol concentrations, and higher systolic and diastolic blood pressure levels.

INSULIN RESISTANCE SYNDROME AND AGEING

These suggest that insulin resistance and hyperinsulinemia are etiologically correlated with the aforementioned cluster ingredients which are defined as the insulin resistance syndrome, syndrome X, or the metabolic syndrome [8]. Elderly persons present greater glucose intolerant and insulin-resistant stances. There is extant polemic as to whether this decrement in functionality is an invariable resultant impact of biological ageing or due to environmental or lifestyle factors, such as augmented obesity, a deranged configuration of fat dissemination, or physical inactivity or deficient exercise evidenced in ageing. It has been shown that these alterable environmental or lifestyle variables culminate in enhanced insulin resistance and hyperinsulinemia, and constitute risk factors for development of metabolic syndrome disorders. Reversal of these untoward states in elderly individuals exhibited improved insulin sensitivity, and glucose tolerance. Adversely, insulin secretion ostensibly declined with age following adjustments for disparities in adiposity, fat distribution, and physical activity [8] or exercise. Despite improvements in lifestyle or other environmental influences, these may contribute to the glucose intolerance evidenced in much older persons [8]. Age-related augmentation in glucose levels is suggested to be associated with aberrant insulin secretion; with sex difference detected with respect to the effect of aging on insulin resistance [11].

An investigation on disparate states of glucose homeostasis in elderly patients as compared to healthy young subjects and young patients with type 2 diabetes intravenous glucose tolerance test suggested that insulin resistance was characteristic of conventional ageing trajectory; with senility as a consequential or invariable risk factor for glucose intolerance and metabolic syndrome with its consequential complications [12]. Insulin secretion and insulin clearance as well as insulin and target tissue interactions were impaired in elderly patients. These functionalities are intermediate between healthy and type 2 diabetic subjects, with predilection of the elderly general population for the risk of deranged glucose tolerance or diabetes with its concomitant vascular sequelae [12].

INSULIN, GLUCOSE TOLERANCE AND AGEING

Glucose tolerance diminishes intermittently with age, and is characterized by high prevalence of type 2 diabetes and post challenge hyperglycemia in the older population. In humans, age-associated glucose intolerance correlates with insulin resistance, but circulating insulin concentrations mimic those younger individuals. In certain presentations of hyperglycemic challenge, insulin is lower in older people, and may be due to β-cell dysfunction. With insulin sensitivity being controlled for, insulin secretory deficit were inevitably detected in ageing [13]. Superimposed on this is the decrement of β-cell sensitivity to incretion hormones with increasing age. In the presence of untoward β-cell compensation to age-related insulin resistance, older individuals may be susceptible to post challenge hyperglycemia and type 2 diabetes. A proper understanding of the metabolic modifications correlated with ageing, provides the latitude for the development of interventions in prevention and therapeutics, especially in a high risk population for glucose intolerance. The interaction of diverse variables associated with ageing, such as augmented adiposity, diminished physical activity or exercise, therapeutics, syndemics, comorbidities and insulin secretory derangement connected with the ageing trajectory, ostensibly contribute to modifications in glucose tolerance [13].

INSULIN, AGEING AND SKELETAL MUSCLE DYSFUNCTION

Age increase is directly proportional to the risk of developing type 2 diabetes; and associated with senile skeletal muscle dysfunctionality. As skeletal muscle ages, mitochondrial deterioration, intramyocellular lipid accumulation, elevated inflammation, oxidative stress, altered activity of insulin sensitivity regulatory enzymes, endoplasmic reticulum stress, diminished autophagy, sarcopenia and over-activated renin-angiotensin system may be enacted. These modifications may tantamount to defective skeletal muscle insulin sensitivity and elevated risk for insulin resistance and type 2 diabetes as skeletal muscle ages [14]. Explicating the process in the enhanced risk of insulin resistance in the ageing of skeletal muscle provides an encompassing understanding for the high incidence of type 2 diabetes in elderly persons, and implements

modalities in the prevention, treatment [14] and management of type 2 diabetes [15-17] in elderly individuals.

INSULIN-LIKE GROWTH FACTOR-1 (IGF-1) AND MITOPHAGY

Mitochondrial defect inevitably signifies cellular ageing [3,18,19]. Mitophagy is a critical mitochondrial quality control mechanism that eliminates dysfunctional mitochondria and aids in cell survival. Insulin-like growth factor 1 (IGF-1) promotes survival of smooth muscle cells (SMCs), but its potential effect on cellular aging is elusive. An antiageing effect was suggested on detection that IGF-1 diminished cell senescence, inhibited DNA telomere shortening, augmented mitochondrial membrane potential, activated cytochrome C oxidase, and minimized mitochondrial DNA derangement in sustained cultured (aged) aortic SMC. IGF-1 enhanced mitophagy in aged cells, and it was associated with mitigated expression of cyclin-dependent kinase inhibitors p16 and p21 and augmented levels of Nrf2 and Sirt3 [20], biogenesis in regulators of mitophagy and mitochondria. SiRNA-induced suppression of either Nrf2 or Sirt3 obliterated IGF-1-induced up regulation of mitophagy. Thus, indicating that the Nrf2/Sirt3 pathway was necessary for the impact of IGF-1 on mitophagy. PINK1 is a prime mitophagy regulator. The silencing of PINK1 suppressed mitophagy and inhibited IGF-1-induced antiageing impacts in aged SMC, as expected with the pertinent function of mitophagy on the impact of IGF-1 in cellular ageing. IGF-1 inhibited cellular ageing via Nrf2/ Sirt3-dependent mitophagy activation [20]. Thus, the findings suggest that IGF-1 signaling activation is a viable potential approach for mitophagy activation and retardation of cellular ageing. Insulin-like growth factor 1 (IGF-1) is an endocrine and autocrine/paracrine growth factor expressed by a vast majority of cells, such as vascular SMC; and has crucial impacts on cell growth, differentiation, and migration. Numerous data indicate that IGF-1 [20,21] sustains mitochondrial functionalities in vitro and in vivo; with cancer cell viability dependent on the stimulation of IGF-1 for mitochondrial biogenesis and mitophagy. A therapeutic potential is essential for IGF-1 in mitophagy stimulation and resultant retardation of cellular ageing [21].

AGEING, INSULIN AND INSULIN SIGNALING

It is suggested from studies of genetic and metabolic features associated with healthy longevity and old age survival that the conserved ancient IIS pathway has a factor in human longevity [22]. Expansive research indicts insulin and insulin signaling in good prognosis for aging and longevity. Studies of insulin and insulin receptors exposed the physiological insulin relevance to the brain. Pathways which influence responses of an organism to modifications in its environment are involved in the genetic regulation of lifespan among disparate species. An established prime pathway via genetic analysis is insulin/insulin-like growth factor-1(IGF-1) signaling (IIS) [23,24]. Insulin/IGF-1-like ligands signal via insulin and IGF-1 receptors. In mammals, insulin/IGF-1 signaling is associated with ageing, lifespan, and longevity [25]. Even though, insulin and IGF-1 function substantially through defined receptors, there exists an expansive overlap and interaction in downstream signaling cascades with resultant problems to estrange impacts of insulin signaling from impacts of IGF-1 signaling. The phenotype of healthy longevity is sustenance of insulin sensitivity [26], as depicted in familial human longevity and the elderly. Insulin effects all the functionalities of human physiology, such as regulation of peripheral glucose homeostasis, crucial contributory neuromodulator to neurobiological processes, undergirds behavioral, cellular, biochemical, and molecular functionalities. Research has depicted the role of type 2 diabetes in premature ageing syndromes, and the elevated incidence of insulin resistance with age [2,18,19].

INSULIN, AGEING, BRAIN AND CANCER

There is expansive empirical evidence that growth hormone and IGF-1 are pertinent for normal development of the bodies and brains of mammals. IGF-1 permeates the blood-brain barrier, and there is extant scientific interest in age-related decrements of serum growth hormones and IGF-1 as mechanisms in effecting cognitive functionality in elderly persons [27]. Mammals and humans exhibit elevated levels of IRs in several brain regions and nuclei, but it is uncertain whether insulin production occurs in the brain. The pathophysiological process of insulin in the brain regarding ageing and longevity are not yet clear. In direct proportionality to global ageing, there is unprecedented acceleration in the prevalence of obesity, metabolic syndrome, type 2 diabetes, and neurodegenerative diseases [2,3,9,15-19]. Insulin resistance is not an uncommon comorbid presentation in these varied aberrations with cardiovascular disorders [3,10]. It is pertinent to understand insulin action for healthy longevity in relation to age-related diseases, perturbations of glucose metabolism, retarded and premature ageing [28].

It is suggested that hyperglycemia and hyperinsulinemia are crucial both in ageing and cancer development. The life elongation impact due to calorie restriction relates to IGF-1 decrement. It is suggested that antidiabetic biguanides are pertinent for both life span prolongation and cancer prevention [29].

INSULIN RESISTANCE, AGEING, OBESITY AND BONE REGULATION

Aging, obesity, and insulin resistance derange bone regulation, leading to imbalance in bone homeostasis and disorder. The conventional debilitative process associated with aging, such as augmented adipogenicity, menopause, andropause and changes in the fate of the mesenchymal stem cell fate. These are potential etiologies of diminished bone density, with consequential osteoporosis, a critical risk factor

of bone fracture in the elderly. Functional restrictions of the aging musculoskeletal system result in limited or restrained physical activity and adverse adipogenicity. Obesity in advanced age results in rapid, aggravated and untoward sequelae, such as impaired health, deteriorated bone health, diminished bone formation, enhanced bone resorption, augmented adipose tissue deposition, deranged bone morphology, and bone liability as well as challenges, issues and opportunities in bone remodeling. The ensuing mechanistic insights per bone homeostasis and interventions for the prognosis of bone quality in aged and obese persons are pertinent measures. Characteristic presentation of skeletal aging with concomitant diminished regulators of bone remodeling dispose to age-related bone dissipation. Obese-insulin resistance leads to untoward impacts in bone remodeling for aged inpatients. Synergistic impacts of obesity and ageing results in adverse rapid bone dissipation. In the aged-obese individual, decrement in BAT, Thy-1 and DOCK7 are etiologic agents of skeletal tissue derangement, requiring prompt and optimum interventions for good prognosis [30].

DISCUSSION

Ageing is associated with perturbed insulin sensitivity and elevated type 2 diabetes prevalence. Evidence in humans indicates that ageing deranges insulin sensitivity independently of modified body composition. It is suggested genetic factors contribute in age-related metabolic dysfunction [31]. The processes of obesity- and ageing-associated insulin resistance are ostensibly disparate, with therapeutic challenges and opportunities for type 2 diabetes in the ageing population. Clinicians need to motivate patients to achieve recommended treatment goals [32] and targets in order to prioritize interventions and programmes for the improvement of care in insulin-ageing sequelae.

Insulin resistance is the hallmark of several ageing-related disorders and morbidities. Insulin is not merely the etiology of belly fat but superimposes on the risk of cardiovascular disease. Among the elderly population, insulin resistance progressively increases with age leading to elevated type 2 diabetes incidence [33].

It is suggested that alterations in body composition and insulin resistance link dysregulation of physiological pathways with resultant obesity and diabetes [34], presentations of premature senescence, and cardiovascular disease risks [2,9,10,34].

Insulin secretion ostensibly decreases with age even after adjusting for disparities in adiposity, fat dissemination, and physical activity [8]. This suggestively contributes to glucose intolerance in the elderly, despite improved lifestyles. There is associated ageing with hyperinsulinemia, but findings are contradictory between modified insulin clearance and insulin secretion. Elevated insulin secretion is the etiology of physiological hyperinsulinaemia in ageing, and not decrement in insulin clearance.

Progressive dissipation of physiological functionality with resultant augmented susceptibility to mortality [7] and morbidity is pathognomonic of ageing. With the advent of ageing, peripheral insulin resistance is progressively enhanced, with concomitant compensatory chronic increases in circulating insulin concentrations. The impact of ageing on insulin secretion suggests that relative insulin secretory derangements are directly proportional to progressive increasing age [7].

Neurological [35], diabetes and obesity impairments in the elderly have their etiologies via a constellation of environmental and genetic variables or gene-environment interactions [2] which are superimposed on conventional age-related alterations [18,19].

Ostensibly, insulin resistance with ageing correlates substantially to lifestyle, for instance, impoverished diet and nutrition, as well as diminished capacity to exercise or physical activity. It is pertinent to control biomarker risk factors [32] in patients with age-related disorders and their sequelae to meet therapeutic targets; and for the elderly not to shirk responsibility in order to attain prolonged and healthier lifespan.

CONCLUSION

Insulin has a crucial role in diverse pathophysiological functionalities in humans, such as brain function in learning and memory, regulation of ageing, metabolic syndrome, obesity, diabetes and cardiovascular disease. Chronic peripheral insulin increase, diminished insulin activity, and decreased brain insulin concentrations are pathognomonic of the insulin resistance syndrome. All these are associated through specific mechanisms in the pathophysiology of insulin and ageing in concert with risk factors and the concomitant sequelae. Ostensibly, progressive excessive insulin induces synchronous elevations in levels of oxidative stress and inflammatory impacts which exacerbate or exacerbated by advancing age. This aggregate of occurrences may pose perturbative repercussions in healthy lifestyle and extended lifespan. Therapeutic interventions may be beneficial to prevent, amend or mitigate insulin derangements in the elderly having age-related conventional ailments.

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