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Ageing Influences Mechanisms Which Perturb Insulin Function with Increased Risk in Morbidity and Mortality

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ABSTRACT

Certain modifications or alterations concomitant with ageing include diminished glucose tolerance due to increased insulin resistance from receptor and/or post-receptor perturbations and decrement in pancreatic islet B-cell sensitivity to glucose. 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 is associated with successful ageing and longevity. This entry enunciates the importance of insulin sensitivity versus secretibility as being critical to the clinical strategy in the treatment, lifestyle changes, early interventions and control of type 2 diabetes. Calorie restriction enhances lifespan in numerous species. Diet manipulation that affects the glucose-insulin system ostensibly benefits lifespan and diminishes the incidence of ageing-related chronic diseases. During ageing, augmented circulating abundance of glucose and other reducing sugars secondary to age-triggered insulin resistance nonenzymatically reacts with proteins and nucleic acids to debilitate tissue elasticity. 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, Insulin Resistance and Sensitivity, Lifespan.

INTRODUCTION

During ageing, the hormone, insulin is the prime 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;

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and lean mammals are less vulnerable to old age disorders as obese ones [1,4]. The mechanisms have not been clearly elucidated, though.

It has been reported that chemical messages from an insulin-like hormone are decreased inside fat cells; while lifespan is enhanced [1,4]. The investigation also highlights the role of insulin in regulation of its synthesis. The inhibition of insulin action within specific cells allows the entire body to maintain a prolonged health, with concomitant retardation of ageing. These result when there is decrement in insulin-like signalling with resultant extension of life expectancy, or 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 effects 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 enhanced susceptibility to mortality. The progressive debilitative process is evident, manifests in all living organisms, 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]. Insulin action is dependent on mechanisms which are determinants of its circulatory levels, 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 life 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 aetiology 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 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

Insulin resistance is untoward biologic response in the stimulation of insulin to target tissues vis-a-vis adipose tissue, liver and muscle. Insulin resistance deranges glucose discharge, with resultant compensatory elevated formation of beta-cell insulin and hyperinsulinemia. The metabolic repercussions of insulin resistance are liable to result in dyslipidemia, endothelial dysfunction, increased inflammatory markers, hyperglycemia, hypertension, hyperuricaemia, prothrombic condition and visceral adiposity. The elucidation of the aetiology and features of insulin resistance as well as the activity of the interprofessional team are pertinent in its management and prognosis [1,4-8]. These suggest that insulin resistance and hyperinsulinemia are aetiologically correlated with the aforementioned cluster ingredients which are defined as insulin resistance syndrome, syndrome X, or 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 [8]. 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. Obversely, 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 differences detected with respect to the effect of aging on insulin resistance [11].

An investigation in 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 of 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 increase in 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 associated with ageing, 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 [14]. 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 implement 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 upregulation 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 anti-ageing 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 has effects in all the functionalities of human physiology, such as regulation of peripheral glucose homeostasis, crucial contributory neuromodulator to neurobiological processes, undergirds behavioural, 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]. Humans and other mammals 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 is 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 aetiologies 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 or fragility 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 bone remodeling regulators dispose of age-related bone dissipation. Obese-insulin resistance leads to untoward impacts in bone remodeling for aged in patients. 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 aetiologic agents of skeletal tissue derangment, requiring prompt and optimum interventions for good prognosis [30]. The prime objective is to enhance and consolidate modifications of lifestyles in these patients. Dietary intervention must incorporate holistic calorie restriction and decrement in high glycemic index carbohydrates. Physical activity or exercise enhances calorie dissipation and insulin sensitivity in muscle tissue.

Ageing, insulin resistance/sensitivity, diabetes and obesity in conspectus

Insulin resistance is a condition whereby a defined concentration of insulin presents a diminished biological

impact. Also, insulin resistance has been permissively related as the requirement of the minimum of 200 units of insulin daily for the attainment of glycemic control and prevention of ketosis. The insulin resistance syndromes present expansive clinical spectra inculcating metabolic syndrome, diabetes, obesity glucose intolerance, and a dire insulin-resistant state [31]. A vast majority of these disorders are associated with diverse metabolic, endocrine, and genetic states. Furthermore, these syndromes may be associated with certain immunologic disorders, and depict unique phenotypic features. The metabolic syndrome, an insulin- resistance condition known as syndrome X or the dysmetabolic syndrome is of immense public health and clinical significance. Patients presenting with diabetes, obesity and high blood pressure have untoward responses to insulin [32,33], and may develop with aging. Insulin resistance fosters diabetes pathophysiology and constitutes a hallmark of obesity, metabolic syndrome, and numerous cardiovascular disorders [34-36]. Thus, the abundance of insulin sensitivity and/or resistance is of immense significance in basic science, clinical practice and epidemiological instances. The methods employed in the determination of insulin sensitivity incorporate hyperinsulinaemic-euglycaemic and hyperglycaemic clamps as well as intravenous glucose tolerance tests [37]. Numerous hormones and regulatory factors impact on insulin action with possible contributary influences in insulin resistance exhibited in obesity. Furthermore, abnormal free fatty acid metabolism is essentially involved in insulin resistance and the aberrant carbohydrate metabolism depicted in obese or diabetic individuals. Thus, the underlying mechanisms involved in the aetiology of insulin resistance are multidimensional and incorporate the insulin signalling pathway. Ageing is associated with augmented bodyweight and fat mass [38,39]. Abdominal fat is not merely related to hyperinsulinaemia, but visceral adiposity correlates with, and is directly proportional to insulin resistance. As obesity is an inducer for diabetes associated insulin resistance, obese individuals present higher concentrations of non-esterified fatty acids, glycerol, hormones, and pro-inflammatory cytokines which may contribute to the aetiopathogenesis of insulin resistance when discharged by adipose tissue [40]. The modifications of/ alterations in body composition due to ageing by diet and exercise training may retard the onset of insulin resistance. Weight dissipation, aerobic and resistive exercise training lead to excoriation of total body and abdominal fat [41,42]. Bodyweight excoriation enhances insulin sensitivity with improvement in glucose tolerance. Moreover, the insulin resistance exhibited in aged individuals are modifiable via physical training or exercise. Significant improvements have been detected in glucose metabolism due to physical training or exercise in middle-aged and elderly persons. The successes in insulin sensitivity with resistive training are directly proportional to improvements in aerobic exercise. Improvements in glucose metabolism following bodyweight dissipation and exercise training may be attributable to alterations in body composition and decrement in total and central body fat. Additional alterations in skeletal muscle [30], blood flow and certain mechanisms possibly interact in the modification of insulin resistance with exercise training. Lifestyle changes, bodyweight excoriation and physical activity are functional and beneficial health provisions [35,36] for the enhancement of insulin sensitivity and prevention of glucose intolerance and type 2 diabetes during ageing.

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 that genetic factors contribute in age-related metabolic dysfunction [43]. 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 [44] and targets to prioritize interventions and programmes for improving care in insulin-ageing sequelae.

Insulin resistance is the hallmark of several ageing-related disorders and morbidities. Insulin is not merely the aetiology 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 [45].

It is suggested that alterations in body composition and insulin resistance link dysregulation of physiological pathways with resultant obesity and diabetes [46], presentations of premature senescence, and cardiovascular disease risks [2, 9, 10, 47].

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 aetiology 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 [48], diabetes and obesity impairments [49] in the elderly have their aetiologies 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 [44] in patients with age-related disorders and their sequelae to meet therapeutic targets [16,17,49,50]; and for the elderly not to shirk responsibility in order to attain prolonged and healthier lifespan [51].

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. The 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.

REFERENCES

1. Hwangbo DS, Gersham B, Tu M-P, Palmer M, Tatar M. (2004). Drosophila dFOXO controls lifespan and regulates insulin signalling in brain and fat body. Nature. 429(6991):562-566.
2. Chukwuma Sr C. (2014). Is Diabetes a Model for Gene-environment Interaction in Premature Senescence? Journal of Biology, Agriculture and Healthcare. 4(25):84-90.
3. Chukwuma Sr C, Tuomilehto J. (1998). The 'thrifty' hypotheses: Clinical and epidemiological significance for non- insulin-dependent diabetes mellitus and cardiovascular disease risk factors. J Cardiovasc Risk. 5(1):11-23.
4. Bai H, Kang P, Tatar M. (2012). Drosophila insulin-like peptide-6 (dilp6) expression from fat body extends lifespan and represses secretion of Drosophila insulin-like peptide-2 from the brain. Aging Cell. 11(6):978-985.
5. Yang F, Xiu M, Yang S, et al. (2021). Extension of Drosophila Lifespan by Astragalus polysaccharide through a Mechanism Dependent on Antioxidant and Insulin/IGF-1 Signaling. Evid Based Complement Alternat Med. 2021:6686748.
6. Keshavarz M, Xie K, Schaaf K, et al. (2022). Targeting the "hallmarks of aging" to slow aging and treat age-related disease: fact or fiction? Mol Psychiatry. DOI: 10.1038/s41380-022-01680-x.
7. Kurauti MA, Soares GM, Marmentini C, Bronczek GA, Branco RCS. (2021). Insulin and aging. Vitam Horm. 115: 185-219.
8. Muller DC, Elahi D, Tobin JD, Andres R. (1996). The effect of age on insulin resistance and secretion: a review. Semin Nephrol. 16(4):289-298.
9. Chukwuma Sr C. (2017). Syndemics of chronic and acute diseases in vulnerable populations. Acta Medica Scientia. 04(01). www.asdpub.com/index.php/ams.
10. Chukwuma Sr C. (2019). Co-morbid presentations and coronary heart disease risks with type 1 diabetes mellitus. Austin Medical Sciences. 4(2):1037.
11. Oya J, Nakagami T, Yamamoto Y, et al. (2014). Effects of Age on Insulin Resistance and Secretion in Subjects without Diabetes. Intern Med. 53(9):941-947.

12. Refaie MR, Sayed-Ahmed N, Bakr AM, et al. (2006). Aging is an Inevitable Risk Factor for Insulin Resistance "Arabic Abstracts". Journal of Taibah University Medical Sciences. 1(1):A3.

13. Chang AM, Halter JB. (2003). Aging and Insulin Secretion. AJP Endocrinology and Metabolism. 284(1):E7-E12.

14. Shou J, Chen P-J, Xiao W-H. (2020). Mechanism of increased risk of insulin resistance in aging skeletal muscle: Diabetology & Metabolic Syndrome. 12(1):14.

15. Chukwuma Sr C. (1995). Type II diabetic nephropathy in perspective. Journal of Diabetes & its Complications. 9(1):55-67.

16. Chukwuma Sr C. (2019). Prevalence, awareness, treatment and control of hypertension amongst non-diabetic and Type 2 diabetic patients in Finland (1987-1997). Journal of molecular pharmaceuticals and regulatory affairs. 2:14-24.

17. Chukwuma Sr C. (2018). Convergence on the constraints and challenges in the awareness, prevention, treatment and control of type 2 diabetes and related conditions. GJMR. 17(3):9-16.

18. Chukwuma Sr C. (2020). Aging, cellular senescence and diabetes mellitus: Clinicopathological correlates, trends and targets. Arch Health Sci. 4(1):1-10.

19. Chukwuma Sr C. (2020). The burden of access to insulin analogues in vulnerable populations. Adv Res Endocrinol Metab. 2(1):68-73.

20. Hou X, Li Z, Higashi Y, Delafontaine P, Suhkanov S. (2020). Insulin-like Growth Factor Prevents Cellular Aging via Activation of Mitophagy. J Aging Res. 2020:4939310.

21. Markaki M, Palikaras K, Tavernarakis N. (2018). Novel insights into the anti-aging role of mitophagy. Int Rev Cell Mol Biol. 340:169-208.

22. Diana van Heemst. (2010). Insulin, IGF-1 and longevity. Aging and disease. 1(2):147-157.

23. Holzenberger M, Dupont J, Ducos B, Leneuve P, Geloen A, Even PC, et al. (2003). IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. Nature. 421(6919):182-187.

24. Iser WB, Gami MS, Wolkow CA. (2007). Insulin signaling in Caenorhabditis elegans regulates both endocrine-like and cell-autonomous outputs. Dev Biol. 303(2):434-447.

25. Bartke A, Chandrashekar V, Dominici F, Turyn D, Kinney B, Steger R, et al. (2003). Insulin-like growth factor 1 (IGF-1) and aging: controversies and new insights. Biogerontology. 4(1):1-8.

26. Fulop T, Larbi A, Douziech N. (2003). Insulin receptor and ageing. Pathol Biol. 51(10):574-580.

27. Sonntag WE, Ramsey M, Carter C. (2005). Growth hormone and insulin-like growth factor-1 (IGF-1) and their influence on cognitive aging. Ageing Res Rev. 4(2):195-212.

28. Akintola AA, van Heemst D. (2015). Insulin, Aging, and the Brain: Mechanisms and Implications. Front Endocrinol (Lausanne). 6:13.

29. Anisimov VN. (2003). Insulin/IGF-1 signaling pathway driving aging and cancer as a target for pharmacological intervention. Exp Gerontol. 38(10):1041-1049.

30. Imerb N, Thonusin C, Chattipakorn N, Chattipakorn SC. (2020). Aging, obese-insulin resistance, and bone remodeling. Mech Ageing Dev. 191(Suppl. 1):111335.

31. Freeman AM, Pennings N. (2022). Insulin Resistance. [Updated 2022 Jul 4]. In: Stat Pearls [Internet]. USA: Treasure Island (FL): StatPearls Publishing.

32. De Fronzo RA, Ferrannini E. (1991). Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care. 14(3):173-194.

33. Reaven GM. (2005). The insulin resistance syndrome: definition and dietary approaches to treatment. Annu Rev Nutr. 25:391-406.

34. Hossan T, Kundu S, Alam SS, Nagarajan S. (2019). Epigenetic Modifications Associated with the Pathogenesis of Type 2 Diabetes Mellitus. Endocr Metab Immune Disord Drug Targets. 19(6):775-786.

35. Chukwuma Sr C. (2022). Characterization of the Clinical and Molecular Perspectives of Epigenetics. Archives of Clinical Investigations. DOI: 10.31579/aci.2022/003.

36. Chukwuma Sr C. (2022). Epigenetics and its essence in understanding human growth, development and disease. J Med Res. 8(5):165-172.

37. Muniyappa R, Lee S, Chen H, Quon MJ. (2008). Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab. 294(1): E15-E26.

38. Haddad J, Haddad FH, Nasser R, et al. (2014). Biphasic Insulin Aspart 30 Therapy in Insulin-Naïve and Insulin-Experienced Patients with Type 2 Diabetes: Results from the Jordanian Subgroup of the A1chieve. Journal of Diabetes Mellitus. 4(4):51841.

39. Cheung KC, Leung HY, Ko KM. (2020). A Unifying Theory of Aging between Modern Medicine and Traditional Chinese Medicine. J Chinese Medicine. 11(2):100921.

40. Wondmkun YT. (2020). Obesity, Insulin Resistance, and Type 2 Diabetes: Associations and Therapeutic Implications. Diabetes Metab Syndr Obes. 13:3611-3616.

41. Ryan AS. (2000). Insulin Resistence with Aging: Effects of Diet and Exercise. Sports Med. 30(5):327-346.

42. Ryan AS. (2010). Exercise in aging: its important role in mortality, obesity and insulin resistance. Aging Health. 6(5).

43. Ehrhardt N, Cui J, Dagdeviren S, et al. (2018). Adiposity-Independent Effects of Aging on Insulin Sensitivity and Clearance in Mice and Humans. Obesity (Silver Spring). 27(3):434-443.

44. Kianmehr H, Zhang P, Luo J, et al. (2022). Potential gains in life expectancy associated with achieving treatment goals in US adults with type 2 diabetes. JAMA Netw Open. 5(4):e227705.

45. Settano R, Villar M, Gallardo N, et al. (2009). The effect of aging on insulin signalling pathway is tissue dependent: Central role of adipose tissue in the insulin resistance of aging. Mech Ageing Dev. 130(3):189-197.

46. Chia CW, Egan JM, Ferrucci L. (2018). Age-Related Changes in Glucose Metabolism, Hyperglycemia, and Cardiovascular Risk. Circ Res. 123(7): 886-904.

47. Chukwuma Sr C. (2020). An overview of the neurological consequences of obesity and diabetes. Journal of neuroscience and neuropsychology. 3:106.

48. Chukwuma Sr C. (2019). Regulatory and metabolic interactions of carbohydrates and lipids in diabetes and obesity. J Biotech Res. 5(11):123-127.

49. Chentli F, Azzoug S, Mahgoun S. (2015). Diabetes mellitus in elderly. Indian J Endocrinol Metab. 19(6):744-752.

50. Longo M, Bellastella G, Maiorino MI, et al. (2019). Endocrine Frailty in the Elderly. Diabetes and Aging: From treatment goals to pharmacologic therapy. Front. Endocrinol. 2019: 00045.

51. Chukwuma Sr C. (2018). Type 1 diabetes mellitus: Issues, challenges and opportunities. Edelweiss Applied Science and Technology. 2(1):290-297.