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Understanding the aetiologies, pathogenesis, evaluation and management of ageing and insulin

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Abstract

This article presents the essence of insulin sensitivity, secretion and resistance in the treatment, lifestyle modifications, interventions and control of diabetes, obesity and related disorders . Progressive decline of glucose tolerance with advanced age is associated with the pathogenesis of type 2 diabetes due to peripheral insulin resistance and impaired β cell function. In elderly persons, insulin secretion is impaired with decreased insulin clearance rate and increased circulating proinsulin concentration that suggests age-related hyperglycaemia. Insulin is associated with numerous pathophysiologic mechanisms during brain functionality, learning and memory, as much as in the regulation of ageing, metabolic syndrome, obesity, diabetes and cardiovascular diseases in Man. Elevated chronic peripheral insulin, decreased insulin action and brain insulin levels are pathognomonic of the insulin resistance syndrome. These are entirely associated by means of defined mechanisms in the pathophysiology of ageing and insulin in concert with risk factors and concomitant complications. Suggestively, progressive excess insulin potentiates synchronous elevated levels of oxidative stress and inflammatory effects which exacerbate or are aggravated by advancing age, leading to inimical consequences of healthy lifestyles, longevity or extended lifespan. Therapeutics and other healthcare measures may be beneficial to prevent, mitigate or amend insulin aberrations in the elderly and during the ageing process. The mainstay in the management of the elderly patient with perturbed insulin function is control of therapeutic application, as it is capable of reverting acute terminal conditions. Treatment necessitates stringent and ardent expertise, knowledge and skills for optimum provision and effective cerebral, cardiovascular and skeletal protection for a healthier lifespan and longevity. This article contributes to the understanding of the prevention, treatment and control of insulin resistance, metabolic syndrome, diabetes, obesity, cardiovascular and neurological disorders during ageing.

Keywords: Gut-brain axis; Bone and skeletal muscle; Neurological disorders; Cardiovasculardiseases; Obesity; Diabetes; Insulin resistance and sensitivity; Mitochondrial effects

1 Introduction

This study contributes to the understanding of the aetiology, prevention, treatment and control of insulin resistance and sensitivity, metabolic syndrome, diabetes, obesity, cardiovascular and neurological disorders, especially in the elderly. Changes related with ageing include reduced glucose tolerance pertaining to elevated insulin resistance due to receptor and/or post-receptor impairments and decreased pancreatic islet B-cell sensitivity to glucose [1]. The hormone, insulin influences ageing and lifespan as well as proffers a mechanism in gene manipulations in the prolongation of lives and healthier lifestyles, even as preserved insulin. Insulin functionality is reliant on mechanisms which potentiate its circulating concentrations, secretion, clearance and sensitivity in its target tissues. Ageing exerts untoward effects on these processes which debilitate insulin functionality, resulting in elevated risk for untoward complications, morbidity, and mortality [1]. Models of aberrant insulin signaling are related to prolonged longevity or resistance to life-threatening factors, such as oxidative stress [1-3]. Insulin and insulin signaling correlate with

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successful ageing and longevity. This article argues the significance of insulin sensitivity versus secretion in the clinical strategy for treatment, lifestyle modifications, prompt interventions in type 2 diabetes control [1-5]. Calorie restriction promotes lifespan in several species [3]. Diet manipulation that influences the glucose-insulin system promotes lifespan and decreases the propensity for ageing-related chronic disorders. As ageing progresses, circulating levels of glucose and certain reducing sugars secondary to aged-induced insulin resistance nonenzymatically react with proteins and nucleic acids to degrade tissue elasticity. The control of factors related to risks for obesity, diabetes, cardiovascular disease, as well as other insulin and ageing sequelae may be mitigated during the ageing process for prolonged longevity and lifespan [5-7].

2 Mechanism and characterization of insulin and ageing

With ageing progression, the hormone, insulin constitutes the prime component that potentiates glucose uptake by cells from the blood stream. As calorie restriction enhances longer lifespan, controlled famine [1-5] perspicaciously maintains mammalian lifespan; with lean mammals being less susceptible to ageing disorders in comparison to the obese [1, 4].

Chemical messages from an insulin-like hormone are diminished within fat cells during lifespan enhancement [1, 4]. The role of insulin in the regulation of its own synthesis, and inhibition of insulin action inside certain cells permit the body to maintain a prolonged health, with simultaneous retardation of ageing. These occur during (I) reduced insulin-like signaling resulting in extension of life expectancy,(ii) as either the insulin-like receptor (InR); (iii) its receptor substrate mutates, or (iv) ablation of insulin-producing cells [1, 2]. Even though, it is not specific when insulin effects ageing, insulin independently achieves the effect, regulates its own production, and regulates tissue ageing directly. Invariably, low insulin levels promote stronger and healthier cells for the prevention of infections and age-related diseases [5, 6].

Ageing regulation is a complex physiological mechanism involving secretion of hormones, nutritional inputs, and metabolic regulation. Ageing characterization inculcates intermittent loss of physiological function resulting in enhanced vulnerability to mortality. The progressive deranging process is evidentially manifests in all biota, and constitutes the limiting risk factor for untoward conditions, such as obesity, diabetes, neurodegenerative and cardiovascular aberrations.

Numerous age-associated disorders are inextricably-linked with imbalance of insulin action. Insulin and IGF1 receptors mediate their effects in the regulation of cell proliferation, differentiation [7], metabolism, growth [6] and development. Insulin functionality depends on mechanisms which determine its circulatory abundance, secretion, clearance and sensitivity in target cells or tissues. Ageing debilitaties these mechanisms which result in impaired insulin action with resultant increased risk in complications, morbidity and mortality. Improved insulin action is pertinent for healthier and longer life span [7] and life expectancy.

Insulin resistance is an inimical biologic response for insulin stimulation in target tissues, such as adipose tissue, liver and muscle. Insulin resistance derails glucose discharge with concomitant compensatory augmented beta-cell insulin and hyperinsulinaemia production. The metabolic consequences of insulin resistance may lead to dyslipidemia, endothelial impairment, aggravated inflammatory markers, hyperglycaemia, hypertension, hyperuricaemia, prothrombic status and visceral adiposity. The aetiology and characteristics of insulin resistance in conjunction with the activity of a multipurpose healthcare team are requisite parameters for management and prognosis [1, 4-8]. Thus, insulin resistance and hyperinsulinaemia may be aetiologically associated with the aforementioned cluster ingredients defined as the insulin resistance syndrome, syndrome X, or the metabolic syndrome [8]. Elderly subjects depict higher glucose intolerant and insulin-resistant conditions. Extant controversy as to whether this ameliorated function is an invariable resultant effect 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 hyperinsulinaemia, and constitute risk factors for development of metabolic syndrome disorders. Reversal of these aberrant conditions presented in elderly individuals improved insulin sensitivity, and glucose tolerance. Conversely, insulin secretion, apparently progressively declined with age following adjustments for differences in adiposity, fat distribution, and physical activity [8] or exercise. Despite improvements in lifestyle or other environmental effects, these could be contributary to the glucose intolerance depicted in older individuals. Age-related elevation of glucose concentrations suggested association with untoward insulin secretion; with detected sex differences regarding the impacts of ageing on insulin resistance [9].

Disparate states of glucose homeostasis in elderly patients in comparison to healthy young subjects and young patients having type 2 diabetes intravenous glucose tolerance test indicated that insulin resistance was characterised conventional ageing, in concert with senility as a consequential or invariable risk factor for glucose intolerance and metabolic syndrome with its consequential sequelae [10]. Insulin secretion and clearance with insulin and target tissue interactions were debilitated in elderly subjects. These functions are intermediate between healthy and type 2 diabetic patients, with generality of the elderly population susceptible to the risk of impaired glucose tolerance or diabetes with its concomitant vascular complications.

3 Obesity, skeletal muscle and impaired bone regulation

Obesity is a model for rapid ageing, and it is associated with peripheral insulin resistance, deficient adiponectin concentration, and enhanced chronic inflammation [11]. Ageing, obesity, and insulin resistance impair bone regulation, resulting in disequilibrium of bone homeostasis and disease. The usual deleterious mechanism associated with ageing, such as elevated adipogenicity, menopause, andropause and alterations in the status of the mesenchymal stem cell. These constitute potential aetiologies of reduced bone density and consequential osteoporosis, as a critical risk factor of bone fracture in elderly persons. Functional limitations of the ageing musculoskeletal system lead to restrained physical activity and aggravated adipogenicity. In advanced age, obesity results in accelerated, adverse and aberrant complications, such as deranged health, fragile bone health, impaired bone formation, augmented bone resorption, rapid adipose tissue deposition, debilitated bone morphology, and bone fragility as including challenges and issues in bone remodeling. The presenting mechanistic insights in bone homeostasis and interventions for bone quality and prognosis in aged and obese individuals are critical measures. The features of skeletal ageing with ensuing limited bone remodeling regulators dispose to age-related bone loss. Obese-insulin resistance exerts aberrant effects in bone remodeling for aged inpatients. Synergistic effects of obesity and ageing result in rapid and aggravated bone loss. Aged-obese individuals present decreased BAT, Thy-1 and DOCK7 as aetiologic agents of skeletal tissue deterioration which necessitate early and optimum interventions for excellent prognosis [11]. The prime goal is enhancement and consolidation and modification of lifestyles in the patients. Dietary intervention needs to be holistically incorporated with calorie restriction and restrictions in carbohydrates high glycaemic index. Physical activity and exercise augments calorie loss and insulin sensitivity in muscle tissue.

Age increases in direct proportion to the risk of type 2 diabetes development; and it is associated with senile skeletal muscle dysfunction. During skeletal muscle ageing, mitochondrial debility, intramyocellular lipid accumulation, increased inflammation, oxidative stress, modified functionality of insulin sensitivity regulatory enzymes, endoplasmic reticulum stress, limited autophagy, sarcopenia and over-activated renin-angiotensin system may occur [12]. These alterations tend to culminate in impaired skeletal muscle insulin sensitivity and increased risk for insulin resistance and type 2 diabetes during ageing of skeletal muscle. Understanding the process in the elevated risk of insulin resistance in the ageing of skeletal muscle provides an expansive latitude to explicate the high incidence of type 2 diabetes in elderly persons, to evaluate and monitor the prevention, treatment [12] and type 2 diabetes management [13-15] in elderly patients.

Glucose tolerance decreases intermittently with age, and is characterized by high type 2 diabetes prevalence and postchallenge hyperglycaemia among the elderly population. Age-associated glucose intolerance relates to insulin resistance, but circulating insulin levels are similar to those of younger persons. During certain hyperglycaemic episodes, insulin is diminished in elderly persons, and ostensibly due to β-cell dysfunction. When insulin sensitivity is controlled for, insulin secretory deficit can be determined during ageing [16-18]. Concomitantly, there is diminished β-cell sensitivity for increase in hormones with advancing age. With aberrant β-cell compensation to age-related insulin resistance, older persons may become vulnerable to postchallenge hyperglycaemia and type 2 diabetes. There are needs for interventions in prevention and therapeutics, particularly in a high risk population for glucose intolerance. The interaction of several factors associated with ageing, such as enhanced adiposity, restricted physical activity and exercise, therapeutics, syndemics, comorbidities and insulin secretory deterioration associated with ageing, tend to contribute in the alterations of glucose tolerance [16-18].

4 Type 2 diabetes and cardiovascular impacts

Ageing correlates with a high incidence of hypertension, type 2 diabetes, and coronary heart disease. Diverse polemics underly the common mechanism [8] in the aetiology of the disorders as to present in syndemics [19], comorbidities [20], or frequent clustering in the same person [8]. Insulin resistance and/or hyperinsulinaemia correlate with glucose intolerance, dyslipidaemia manifesting as increased plasma triglyceride and diminished high-density lipoprotein-cholesterol contents, and higher systolic and diastolic blood pressure levels.

Insulin resistance in type 2 diabetes and obesity constitutes a major risk factor for cardiovascular anomaly. Insulin forms a crucial therapeutic component for blood glucose management in diabetes. Insulin may be critical for normal cardiovascular function, and it's deficit depicted in insulin resistance culminates in cardiovascular impairment and disorder. Insulin is a prime ingredient of glucose-insulin-potassium cocktail with crucial protective influence through phosphatidyl 3'-kinase-protein kinase-protein B-endothelial nitric oxide synthase, PI 3K-Akt-eNOS dependent signalling process in combination with its metabolic modulation that conversation it with effective organ protector as applicable in numerous clinical interventions in health and disease [21-23].

Hypertestosteronamia may be involved in states of insulin in resistant pathogenesis and androgen replacement therapy, thereby rendering importance to glycaemic control and cardiovascular risk, as particularly evident in diabetic male subjects [24, 25].

5 Therapeutic interventions and other healthcare measures

There is progressive derangement in β-cell function in type 2 diabetes irrespective of the type of treatment. Persistence hyperglycemia causes progressive decline of β-cell functionality with resultant β-cell exhaustion and culminating in β-cell excoriation and dysfunctionality. Type 1 diabetes constitutes an autoimmune state with a remarkable inherited stance, and an increasing global incidence [26-28] Approximately 25% of these cases are diagnosed in early adulthood and into advanced age [28]. The improvements in care and decline in mortality rate have been attributed to the increase of elderly persons presenting with type 1 diabetes. There is a paucity of clinical trials in persons older than 70 years of age having type 1 diabetes with comorbidities, dependency and frailty. Type 1 diabetes management and the therapeutic objectives must be personalized according to the health status and life expectancy of the patient. With regard to healthier elderly patients, insulin treatment regimens inculcating multiple insulin injections or insulin pump therapy on a daily basis which approximate normal physiological insulin secretion ought to be employed in order to achieve lower glycaemic goals, with concomitant reduction in hypoglycemic risk, and frequent glucose monitoring with preferential application of continuous glucose monitoring systems [29, 30]. It is appreciable to apply less stringent glycaemic targets and insulin regimens in frail persons with poor prognosis or health. Ageing disorders, such as poor cognition, hearing and vision as well as depression, chronic pain and defective mobility may impede intricate insulin regimens. In such instances, the prime therapeutic objective would be ameliorating the acute hyperglycemia impacts, mitigating hypoglycemic risk, and optimizing quality of life [30]. Newfangled insulin preparations and advanced technology in insulin delivery and monitoring of blood glucose have contributed to augmented management of type 1 diabetes in all age groups.

Insulin resistance is a common characteristic of ageing, accompanied with loss of gonadal function in female persons due to decreased plasma estrogen abundance. Diverse aetiologies have been attributed for this insulin resistance, such as alterations in steps of the insulin pathway [31]. Findings indicate that 17β-estradiol treatment can ameliorate the deranging impact of ageing on insulin sensitivity, in the minimum, at the plasma membrane level localized Glut4; with further research methodology required to elucidate it [31].

6 Fitness concerns and metabolic health

The ageing process and ageing are inextricably-linked with deteriorated insulin sensitivity and high type 2 diabetes prevalence. Ageing deranges insulin sensitivity independently of modified body composition in humans; and genetic factors contribute in age-related metabolic dysfunction [32]. Obesity- and ageing-associated insulin resistance are ostensibly distinct for therapeutics for type 2 diabetes in the ageing population. There is a pertinent requirement for healthcare professionals to motivate patients and achieve the recommended treatment goals [33] and targets to prioritize interventions and programmes to improve care in insulin-ageing and its sequelae.

Insulin resistance is the hallmark of diverse ageing-related conditions. Insulin does not merely constitute the aetiology of belly fat but aggravates the risk of cardiovascular diseases. In older age groups, insulin resistance progresses with increased age resulting in enhanced type 2 diabetes incidence [34]. Changes in body composition and insulin resistance correlate with dysregulation of physiological pathways culminating in obesity and diabetes [35], premature senescence, and cardiovascular disease risks [2, 9, 10, 36]. Insulin secretion suggestively diminishes with age even after adjusting for differences in adiposity, fat distribution, and physical activity [8] and exercise. This may contribute to glucose intolerance in the elderly, irrespective of improved lifestyles. Ageing is associated with hyperinsulinemia, but results are controversial between altered insulin clearance and insulin secretion. Increased insulin secretion is the aetiology of physiological hyperinsulinaemia in ageing, and not reduction in insulin clearance.

Progressive loss of physiological function with resultant enhanced susceptibility to mortality [7] and morbidity is pathognomonic of the ageing mechanism. During ageing, peripheral insulin resistance is progressively heightened with compensatory chronic increases in circulating insulin levels. The exerting effect of ageing on insulin secretion indicates that relative insulin secretory disruptions are invariably connected to progressive ageing [7]. Neurological disorders [37], diabetes and obesity [38] in the elderly have their aetiologies via a constellation of environmental and genetic factors or gene-environment interactions [2] which are exerted on usual age-related modifications [17, 18].

Ostensibly, insulin resistance with ageing correlates critically to lifestyle, for instance, poor diet and nutrition, including diminished capacity to exercise or physical activity. It is crucial to control biomarker risk factors [33] in subjects with age-related conditions and their complications to achieve therapeutic targets and goals [14, 15, 38, 39]; and for the elderly to adhere responsibly to indications for attainment of prolonged and healthier lifestyle and lifespan. The shift in age distribution in the elderly and progressive ageing in several populations correlate to epidemic of obesity and its associated metabolic sequelae, such as, type 2 diabetes. Adipose tissue (AT) impairment is pathognomonic of the ageing process with resultant systemic metabolic alterations. Insulin resistance, ectopic lipid accumulation and chronic inflammation are implicated for elevated risk of obesity and type 2 diabetes onset correlated to ageing. Conversely, obesity and type 2 diabetes, pathognomonic of AT impairment, exhibit identical physiologic characteristics as ageing, such as increased burden of senescent cells and epigenetic changes. These chronic metabolic aberrations suggestively relate to a condition of accelerated or premature ageing [40-44]. Progressively, chronic insulin resistance may culminate in prediabetes and in type 2 diabetes due to deficient treatment or persistent incurability [45-46].

7 Discussion

Recent data and trends indicate that hyperinsulinaemia development precedes insulin resistance [47]. Gene-environment interactions [3], over-nutrition, processed diet consumption and other related factors tend to elevate insulin secretion, diminish insulin pulses, and/or decrease hepatic insulin clearance resulting in hyperinsulinaemia, especially in the aged. Hyperinsulinaemia causes the imbalance in the insulin-GH-IGF axis with resultant shift in the insulin:GH ratio directed at insulin with a departure from GH. The shift in insulin-GH augments lipid synthesis, storage of energy, and suppresses breakdown of lipids culminating in obesity due to aggravated accumulated fat and increased adipose tissue and concomitant inhibition in lipid breakdown and diminished energy expenditure [47-49]. Hyperinsulinaemia constitutes a critical aetiopathogenetic factor in type 2 diabetes, obesity, metabolic syndrome, cardiovascular disease, neurodegenerative disorders and premature death. Ostensibly, nutritionally enhanced insulin exposure influences ageing. The interventions which normalize and/or diminish plasma insulin levels, contribute towards the prevention, treatment and control of age-associated progressive decline and other related diseases. Calorie restrictions, augmentation of hepatic insulin clearance, maximization of insulin sensitivity may play vital roles in the management of hyperinsulinaemia in the elderly and general population. Suggestively, these retard age-associated physiologic depreciation and disorders. Therapeutic interventions which ameliorate hyperinsulin secretion, normalize or mitigate pulsatile insulin secretion with enhanced hepatic insulin clearance may influence the prevention or retardation of the progression of hyperinsulinaemia-moderated aberration in early stages for good prognosis in the ageing-insulin sequelae. Investigations have explored the significance of the gut microbiota and bacteria-derived metabolites as prime ingredients in obesity and metabolic health, particularly whereby overnutrition triggers cognitive derangement [50]. There are indications that gut microbiota regulate homeostasis, metabolism, central appetite, food reward signaling and adiposity with the brain as target via the gut-brain axis [51]. The regulation may be associated in obesity pathophysiology in inextricable linkage with metabolic, neural, immune system and endocrine processes. It is pertinent to explore and unravel newfangled therapeutic modalities in the prevention and treatment of obesity [52].

8 Conclusion

This article argues the clinical strategies and mechanisms in the prevention, treatment and control of insulin impairment, metabolic syndrome and other associated disorders during the ageing process in humans. The hormone, insulin impacts on ageing and lifespan, with provision of mechanisms for the manipulation of genes for longevity ad healthier lifestyles. Sustained insulin sensitivity is associated with longevity, and insulin resistance predicts age-related disease occurrence, such as hypertension, coronary heart disease, stroke, cancer as well as brain functionality in learning and memory, regulation of ageing, metabolic syndrome, obesity and diabetes. Ageing progressively diminishes insulin functionality with resultant risk for morbidity, complications and mortality.

Compliance with ethical standards

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