CPQ Medicine (2020) 10:3
Review Article

Aging, Cellular Senescence and Diabetes Mellitus: Clinicopathological Correlates, Trends and Targets

Chrysanthus Chukwuma

CTR Future-Oriented Ltd, Centre for Future-Oriented Studies, Abakaliki, Ebonyi State, Nigeria

*Correspondence to: Dr. Chrysanthus Chukwuma, CTR Future-Oriented Ltd, Centre for Future-Oriented Studies, Abakaliki, Ebonyi State, Nigeria.

Copyright

Received: 29 August 2020

Published: 15 September 2020

Keywords: *Apoptosis; Quality of Life; Lifespan; Therapeutic Regimen; Consequences*

Abstract

Diabetes and aging correlate with identical organ and system perturbations which are enhanced by concomitant molecular processes such as cellular senescence. Age represents a major risk factor for type 2 diabetes mellitus. It is unclear how senescence contributes to diabetes pathogenesis. Thus, available treatment modalities have not targeted the vital area of the disease. Reversal of untoward features of cellular aging represents a formidable trajectory for novel type 2 diabetes therapies where dissipation of pancreatic beta cells is impaired for insulin secretion. Furthermore, appropriate therapeutic modalities require characterization of defined senescent beta cell populations and the spatiotemporal variations of the expression of senescence genes. Aging is a dynamic public health dilemma in the prevailing demographic transitions in which a vast majority of those from the sixth decade of life increase exponentially in populations. Researchers have attempted to explicate senescence mechanisms via the identification of novel factors which interact with aging and age-related disorders in furtherance of treatment management, quality of life and lifespan regarding diabetes and its complications. An elucidation of the fundamental mechanisms which result in aging and research-oriented focus on healthy aging will mitigate numerous socioeconomic and healthcare encumbrance now and in the future for diabetes mellitus and related conditions.

Introduction

Aging and diabetes culminate in similar organ and system derangements which are undergirded by concomitant molecular mechanisms including cellular senescence. Cellular senescence is fundamentally an aging process indicted in several aging-associated disorders, and is markedly causative of tissue impairment. Aggregation of senescent cells results during the aging process, and is observed contextually in diabetes and obesity [1]. Senescent cells are implicated in the pathogenesis of type 2 diabetes via direct effect on the functionality of pancreatic beta cell, adipose tissue impairment, senescence-associated secretory phenotype (SASP) - mediated tissue deterioration. Metabolism and signaling alterations observed in diabetes, such as growth hormone axis aberration, elevated circulating glucose, and dysfunctional lipid metabolism which induce senescent cell production. Suggestively, senescent cells partially constitute a diabetic pathogenic loop, as combined etiologic agent with resultant impact of metabolic alterations and tissue perturbations.1 Aging constitutes a major risk factor for diabetes and several chronic and noncommunicable diseases. Diabetes prevalence, especially type 2 diabetes correlates with increasing age, especially in high income countries of persons aged 60 years and over.

Etiopathological Mechanisms

Aging is a fundamental process involving endothelial dysfunction that affects both diabetic and normal individuals [2]. Aging is an intricate phenomenon associated with a complex variety of molecular metamorphoses depicted by chronic low grade inflammation referred to as "inflammaging". Type 2 diabetes displays diverse attributes of aging which are detected at an accelerated inception or or expansively expressed coupled with inflammaging. Type 2 diabetes patients present with elevated mortality rate linked with an augmented inflammatory score. The SASP constitutes the major origin of inflammaging in both type 2 diabetes and aging. Disparate pathogenic mechanisms associated with progression of type 2 diabetes and development of complications have been inextricably linked to SASP and senescence, specifically, endoplasmic reticulum stress and oxidative stress [3].

Senescence constitutes a cellular response depicted by stable growth abrogation and several phenotypic changes which include a pro-inflammatory secretome. Senescence contributes to normal growth and development, tissue homeostasis sustenance, and restriction of tumour progression as well as the etiological agent of age-linked disorders [4] and diabetes and its sequelae [5]. Diabetes and aging result in identical organ impairment driven by concurrent molecular mechanisms, namely senescence. The phenomena of numerous senescent cells in diverse tissues corresponds with increase in age, diabetes and obesity. Senescent cells have been invariably indicted in insulin resistance generation [6].

Multiple organ system derangement has identical characteristics in diabetes as in normal chronological aging but the frequency depicts at a younger age in diabetes [7]. Diabetic subjects are more susceptible to the acquisition of age-associated co-morbidities, for instance, debility, frailty, Alzheimer's disease, transient cognitive impairment [8], cardiovascular disorder, ocular derangement, and renal impairment, as diabetes replicates a pro-aging condition [9].

Numerous processes or mechanisms are invariably involved in chronological or pathological aging in both normal and diabetic persons, as are evident in this study. Pancreatic beta-cells sustain the glucose contents of the body within a limited scope. During insulin resistance, diabetes may not emerge because the endocrine pancreas has compensatory growth. Impediment on replacement or lifespan decrement may present deranging impacts for glucose homeostasis [10]. Type 2 diabetes manifests due to deficiency in proliferative beta cells response to compensate for exacerbated demand due to insulin resistance and partly from senescent cell accumulation, ostensibly during aging, deranged senescent beta-cell accumulation contributes to dysfunctional glucose intolerance and diabetes as well as decreased assistance to glucose dilemma as senescent beta cells secrete cytokines and chemokines (SASP) which perturb proximal cells. Acute insulin resistance that is elicited by the insulin receptor antagonist S961 or elevated fat diet [11] culminated in expression of aging markers. This suggests that insulin resistance accelerates beta-cell aging, even as transient hyperglycemia induces remarkable altered beta-cell phenotype and dysfunction. Aging is invariably involved in the dissipation of cell homeostasis with restriction of the lifespan of an organism via an enhanced susceptibility to disorders and impaired tissue regeneration. The glucose uptake connected with energy generation for optimum cell survival must be taken into cognizance as a major etiology of the aging process as related to diabetes. TXNIP controls cellular senescence via the inhibition of AKT pathways by direct interaction in the presence of glucose-derived metabolic stress [12]. *In vitro* and *in vivo*, TXNIP regulates AKT-mediated senescence of cells. AKT activation triggers glucose uptake, inducing cellular senescence by inhibition of transcriptional functionality and deficiency of both bradykinin B1 and B2 receptors [13].

The Cell senescence is a profound defense mechanism for the suppression of tumour, and critical in embryonic development, wound healing, aging and age-related disorders. A senescent cell depicts remarkable morphological alterations and dynamic metabolism concurrently with SASP [11]. Cellular senescence is generated by multifarious endogenous and exogenous stressors which prompt senescence [14]. Senescence constitutes a programmed phenomenon for the facilitation of beta-cell functional maturation. Thus, senescence may be associated in beta-cell regeneration, insulin secretion, diabetes development and progression. Senescent cells are in a state of cell cycle cessation but are metabolically dynamic as they secrete inflammatory factors. This SASP triggers chronic inflammation, oxidative stress and reduced nitric oxide bioaccessibility. The intricate interplay between the triad of processes culminate in age- and diabetes-linked cardiovascular derangement [15].

Researchers have demonstrated that the progressive dissipation of a protein, CSB associated with c that affects considerable figures of Europeans induces proliferating cells into non-reversible aging, and constitutes a determinant of senescence or cellular aging [16]. The unavailability of CSB protein/factor or its impairment predisposes to mitochondrial derangement, and clinicopathological features of Cockayne Syndrome, such as premature aging, psychometric deficit, progressive neurological deterioration, photosensitivity and mimetic of the untoward changes in replicative senescence associated with physiological aging. CSB dissipation is induced by epigenetic reversible and regulated modifications of gene expression sustaining the DNA in its native state but impedes its expression at the DNA stage [16]. A molecule that reverses the deficits of Cockrayne syndrome cells of patients attenuates the normal cell disposition to senescence. It is suggested that there is a critical association between accelerated pathological aging, and the CSB protein presents as a veritable factor antagonistic to senescence. Decrement in naive T-cells in conjunction with elevated levels of

memory cells are expected consequences of aging on the adaptive immune system [17]. Immunosuppressive cells subjugate activities of myeloid and and lymphoid effector cells. Aging elicits the regulatory cell activity of the immuno-suppressive network as it affects remodelling of the immune system as aging transpires [18]. In certain events, p14Amf a cellular senescence promoter is associated with type 2 diabetes occurence. HMGA2 and p14Amf functions within the same framework to induce respectively, senescence, proliferation of precursor cells and adipose tissue stem as well as elevated type 2 diabetes risk [19].

Debilitating metabolic attributes as well as oxidized small and dense low density lipoprotein, ox-dmLDL may be contributory to the diminished number and the dysfunctionalities of circulating endothelial progenitors, EPC from normal donors cultured in ox-dmLDL precursors resulted in senescent-like growth termination. This resultant impact was inextricably linked with activation of Akt, p53 aggregation, p21 expression, dephosphorylation of retinoblastoma protein and with diminished protective influence against oxidative perturbation. Also, dissipation of endogenous p53 expression due to small intruding RNA indicates that this unperturbed pathway is pertinent for the occurrence of senescence in the Akt/p53/p21 signaling pathway activation and rapid senescence inception have been detected in EPC from diabetic patients [20]. The dissipation of endogenous p53 in diabetic EPC fails to result in senescence-growth suppression, and necessitates the propensity to produce tube-like structures *in vitro*. These events depict the p53 signaling pathway activation as a pertinent mechanism contributing to der7anged diabetes neovascularization [20]. Notwithstanding the decreased proliferative potential, senescent cells flagrantly display increased metabolic activity, with an augmented glycolytic state, even at elevated oxygen concentrations, as in carcinogenic ambients or cells. The diversion of pyruvate, the ultimate glycolytic product from oxidative phosphorylation culminates in an altered bioenergetic condition due to augmented oxidative stress driven by dysfunctional mitochondrial accumulation. The presenting metabolite shift results in elevated AMP/ATP and ADP/ATP ratios, and to the subsequent activation of AMPK and culminating in p53-mediated growth arrest [21]. It is suggested that metabolic reprogramming is pertinent to drive substantial energy for defined functionalities connected to senescence condition, the SASP and immune response modulation in the microambient of the senescent cell tissue. Irrespective of the comparative abundance of oxygen in the vascular milieu, healthy and potent endothelial cells generate most of their ATP via anaerobic glucose to lactate conversion during diabetic senescence. Nicotinamide adenine dinucleotide, NAD+ is a vital cofactor in mitochondrial energy generation and numerous enzymatic redox reactions. Age-linked decline in NAD+ is indicted as a driving force in multifaceted dimensions of age-related disorders, metabolic, diabetic and neurodegenerative diseases as well as deficiency in cellular defense mechanisms against oxidative stress [22].

Cell senescence has been implicated as a fundamental etiological consequence of type 2 diabetes and its sequelae. Cellular senescence is the restricted capability of human cells to undergo division as depicted via alterations in morphology and gene expression. A study [5] enunciated the implications of telomere attrition, oxidative stress and pertinent factors or variables in diabetes premature senescence. A plethora of human disorders or perturbations have been associated with the regulations and functions of genes. These are fundamental in environmental signal interpretation for the modulation of cells in the functional output of the genome. The aging mechanism depicts the encompassing manifestation of organisms and gene interaction with the internal and external milieu. Aging pertains due to a plethora of mechanisms which include factors, such as diabetes, immune system dysfunction, oxidative injury, magnitude of apoptosis, and telomere attrition. Indivuduals presenting with shorter telomere lengths are vulnerable to premature

senescence or accelerated biological aging, particularly in diabetic subjects as well as glucose intolerance and elevated blood pressure. Untoward social attributes may contribute to excruciating prognosis for diabetic patients in premature senescence or aging [5]. EPCs are circulating immature cells derived from bone marrow with mobilization to the peripheral circulation corresponding to varied stimuli with contribution to vascular homeostasis and compensatory angiogenesis. EPCs regenerate damaged endothelium, facilitate re-endotheliazation, and impede atherosclerotic lesion production. EPCs are deranged in diabetic patients; and elevated glucose concentrations ostensibly augment EPC presence and senescence with resultant development and progression of diabetes sequelae. Cessation of the loop between cell senescence and diabetes via newfangled modalities against DNA oxidative perturbations constitutes a crucial trajectory to prevent or curb diabetes complications [23].

Cellular senescence is an important feature in the onset, development and progression of diabetic nephropathy inculcating DNA derangement, telomere attrition, mitochondrial perturbation, Klotho dissipation, Wnt/beta-canetenin signaling activation, incessant and persistent inflammation, and uremic toxin accumulation [24]. Diabetic nephropathy is an increasingly prevalent and perturbative disorder that is characterized morphologically by degenarative alterations of renal podocytes correlated with variations of foot process excoriation, glomerular basement membrane thickening, endothelial cell damage, and broadening of the mesangial matrix as well as progressive renal perturbation [25]. In diabetic nephropathy patients, peculiarities of accelerated senescence in the glomeruli have been detected. Autophagy is inextricably linked with the senescent phenotype, and ostensibly regulates both apoptosis and senescence with a probable functionality in senescence and autophagy in mediating glomerular damage in diabetic nephropathy and elucidation of SASP in disease progression as in the invariable establishment of podocyte senescence in diabetic nephropathy.

Hyperglycemia-induced retinal oxidative with oxidative stress may induce vascular cell aging resulting in vascular derangement in diabetic subjects; in contrast, physiological aging impacts on primary cells of the retinal pigmented epithelium [26]. Hyperglycemia-induced retinal vasculature impairment and diabetic retina progression are connected to vascular cell senescence emanating from elevated oxidative with nitrative stress.

Diet and Nutrition in the Management of Aging and Diabetes

Aging predisposes persons to chronic and excruciatingly and disparaging cerebrovascular disorders in normal and diabetic persons [27]. The specific etiology of the neuronal deterioration of these anomalies and normal brain aging defies logic. There is beneficial effect of nutrition on cognitive functions that research needs to be developed and broadened in pre-clinical and clinical settings to stem or ameliorate dysfunctionalities in cognitive aging [28] as applicable to diabetic patients. It is suggested that due to the action of oxidative injury in aging and age-related diseases, such as diabetes, it is pertinent to provide oxidized vitamin E metabolites to adequately monitor participant functional antioxidant content to elucidate the resultant impact of oxidative stress on aging [29], diabetes and other age-related impairments.

Recent anthropogenic activities and contemporary lifestyle in affluent societies, provide the latitude for Man to indulge in overconsumption of food. Food overconsumption oftentimes results in metabolic aberrations,

as in visceral fat aggregation, adiposity, insulin resistance and diabetes, particularly with deficient physical activity [30]. Since Man evolved in environments of relatively sparse food supply, he has become adapted to function both physically and cognitively at an elevated level when placed in a food-restricted/fasting condition. Intermittent fasting, IF and periodic fasting, PF have expansive beneficial impacts on numerous disparate health indices, and counteract disease mechanisms, with a better prognosis in age-associated disorders, such as diabetes, cardiovascular disease, carcinogenic and neurological consequences of disorders as in stroke, Alzheimer's disease8 and Parkinson's disease [31]. IF, PF and time-restricted feeding in normal and obese individuals have established efficacy for weight dissipation and good prognosis in multiple health indicators, insulin resistance and risk factor decrement. The cellular and molecular processes of IF for the improvement of health and suppression of disease mechanisms incorporate activation of adaptive cellular stress response signaling pathways which augment mitochondrial disposition, DNA repair and autophagy [31]. In addition, PF drives stem-cell based regeneration and persistent metabolic impacts. In order to establish the efficacy of IF in the improvement of general health management of leading disorders of senescence and aging, it is imperative to conduct randomized clinical trials of IF against PF and isoenergetic continuous energy deprivations in Man [31,32]. Thus, IF may reverse the untoward impacts on health, aging and disease in diabetes and obesity with prognosis of a long lifespan. Diet and nutrition promote the reversal of diabetes and accelerated aging [33] or premature senescence5 associated with chronic disorders.

Endogenous and Exogenous Therapy

SASP emerges as a driver and optimistic therapeutic target for multifarious age-associated states encompassing diabetes, neurodegenerative and carcinogenic disorders. The development of a "SASP Atlas", comprehensively presents a proteomic database of soluble proteins and exosomal cargo SASP factors emerging from multifarious inducers and cell types [34]. Every profile comprises numerous unique proteins including a subset of proteins augmented in each SASP. The outcome is likely to elucidate protein features of SASP and document potential senescence biomarkers to evaluate the encumbrance, initiating stimulus and tissue of senescent cells *in vivo*.

Senolysis and a combined Dasatinib and Quercetin can selectively eradicate senescent cells, but not non-senescent cells, via transient debilitating pro-survival networks which shield them from an auto-apoptotic milieu. It is suggested that interventions to decrease senescent cell encumbrance prolong healthspan and ameliorate age-related disorders [35], such as diabetes. Mitochondria are cell compartments and ubiquitous in eukaryotic cells associating in diverse vital synthetic, metabolic and signaling processes. The mitochondrial unfolded protein response (mtUPR) emanates from mitochondrial reversal of the signal to the nucleus, and sustain mitochondrial protein homeostasis as unfolded and misfolded proteins incessantly accumulate [36]. mtUPR prevents aging-associated functional incapacitation and treat disorders connected with aging. Accumulation of mutated SOD1 in mitochondrial intra-membrane space results in mtUPR, and culminates in fALS progression.

Eradication of senescent beta cells arrests immune-mediated beta-cell derangement and adequately prevents diabetes development. Beta-cell senescence is a major component of type 1 diabetes pathogenesis, and senescent beta-cell annihilation constitutes a newfangled therapeutic strategy for the disease. This is achievable because senescent beta cells, upregulated pro-survival mediator Bc1-3 and NOD mice treatment

with Bc1-2 inhibitors selectively annihilated these cells and did not change the abundance of the immune cell type associated with the disease [37]. Elimination of senescent cells by drug application or by defined cell dissipation of cells expressing the marker p16Ink4a in transgenic mice restored beta-cell functionality. Identical attributes manifested in cultured human beta cells, depicting translational events [38]. Eukaryotic genomes harbor numerous transposable elements which remain partially functional, and transpose in the host genome [39]. There is repression of mobile element activation to obviate untoward impacts, such as gene mutations or chromosome rearrangements. Regulation of transposable elements involve diverse mechanisms inculcating silencing pathways based on small non-coding RNA generation. Silencing results with transposable elemental RNA degradation or DNA sequence targeting by heterochromatin production and resultant transcriptional suppression. The gradual dissipation of heterochromatin in constitutive heterochromatin regions during aging elicits derepression of transposable elements leading to progressive elevated genomic instability and inflammatory response activation [39].

Diabetes has perspicuously become an expansive public health enigma in elderly persons with propensity to exhibit ubiquitous geriatric syndromes, such as debility/frailty, dementia and cognitive aberration, faecal and urinary incontinence, trauma, and polytherapy which affect quality of life and interference in diabetic management. Application of the frailty index in the determination and establishment of deficit accumulation is an appropriate strategy for the identification of elderly persons at risk for expansive vulnerability, trauma, death and other dissociative affects [40] in diabetes and related diseases.

Parkinsonism is a neurodegenerative disorder depicting motor and non-motor neuron lesions with resistant, incessant and persistent progression to fulminating morbidity, socioeconomic and healthcare encumbrance. The pathologic manifestations include dissipation of dopaminergic neurons in the substantia nigra pars compacta (SNpc) in conjunction with aberrant alpha-synuclein (alpha-syn) deposition of cytoplasmic inclusions known as Lewy bodies located in pigmented, brainstem nuclei, and dystrophic neurons in striatal and cortical precincts as Lewy neurites. In diabetic patients, treatment for Parkinson's disease targets improved quality of life and dopaminergic pathways in the decrement of associated motor symptoms and mitigation of the side effects of L-DOPA pharmacotherapy [41]. There is extant significant functionality for dopamine D3 in the initial development and presentation of Parkinsonism in diabetic patients D3R agonist activation enhances dopamine concentration, reduces alpha-syn accumulation, augments secretion of brain-derived neurotrophic factors, alleviates neuroinflammation, ameliorates oxidative stress, enhances neurogenesis in the nigrostriatal pathway, interacts with D3R to decrease Parkinson disease-linked motor neurone systems and mitigates side effects of levodopa, L-DOPA [41].

The optimal glycemic target in elderly diabetic subjects has to be personalized regarding medical history and comorbidities with predilection for drugs which correlate to low risk of hypoglycemia. For type 2 diabetes elderly patients, these include metformin as first-line agent, pioglitazone, dipeptidyl peptidase-4-inhibitors [42] and glucagon-like pepetide-1-receptor agonists. Precautionary measures to obviate hypoglycemic risk necessitates avoidance of insulin secretagogue agents, and if employed, preference must be accorded to short-acting sulfonylureas as gliclazide, or glinides as rapaglinide [43].

Discussion

Aging constitutes an encompassing characteristic exhibited or manifested by all bioorganisms, tissues and cells. In the elucidation of the etiology, consequences and treatment of aging and diabetes, it becomes pertinent to configure sustainable modalities to achieve pertinent goals. However, the persistent challenges and constraints in research, therapeutic regimen, etiology and consequences of the comorbidity in aging and diabetes is the gap in standardized ecological analysis in defining the interaction between mortality and putative risk factors [44,45] in aging and diabetes with its concomitant complications. Artificial intelligence aging biomarkers provide unrestricted presentation of biological processes or mechanisms for newfangled modalities to enact etiologic models via the extraction of critical characteristic and identification of biologicol targets and processes [46] as necessary in aging/senescence and diabetes as well as in the convergence of inordinate research disciplines. Diabetes in the elderly is an unprecedented dilemma to society. The accelerated aging of the global population has constituted immensely to the diabetics epidemics as the elderly comprise an exemplified encumbrance of the diabetes population. The most burdensome aspect of these presenting challenges in inter alia healthcare, quality of life and healthspan is that the elderly component of the diabetes population is projected to accelerate in population size [47] contemporaneously with other age-related diseases. Healthcare professionals and researchers are rigorously putting all measures in place to manage diabetes and its complications, the clinical characteristics and the economic impact [48] in the aging population. The propensity of progressive aging or the chronological aging process in a vast majority of populations with concomitant pandemic of obesity and concomitant metabolic diseases, such as type 2 diabetes has been disseminated in older age groups. Adipose tissue aberration significantly impacts on the aging trajectory culminating in systemic metabolic changes, as depicted in chronic inflammatory disorders, ectopic lipid accumulation and insulin resistance which potentiate obesity risk and type 2 diabetes in the aging process [49]. Type 2 diabetes and obesity, exemplified in adipose tissue perturbation, present several similar physiological features as aging in elevated encumbrance of senescent cells and epigenetic metamorphosis. These instances may present a grim condition of premature or accelerated aging or senescence [5]. Also, mitochondrial derangement characterizes cellular aging. Mitophagy regulates the mitochondria via the eradication of perturbed mitochondria and drives cell sustenance. The maintenance of smooth muscle cells is potentiated by insulin-like growth factor 1, IGF-1. However, its potential impact on cellular aging [50] or senescence remains unelucidated. IGF-1 was found to diminish cell aging, disrupt DNA telomere dissipation, elevate mitochondrial membrane capacity and capability and cytochrome c oxidase activation as well as mitigation of mitochondrial DNA injury in aged or derelict cultured aortic smooth muscle cells. IGF-1 augmented mitophagy in long-term cells with concomitant diminished expressions of cyclin-dependent kinase inhibitors p16 and p21 and elevated concentrations of Nrf2 and Sirt3, regulatory mechanisms of mitophagy and mitochondria biogenesis. The limiting factor was that SiRNA inhibited Sirt3 or Nrf2 with consequent obliteration of IGF-1-mobilised mitophagy upregulation. It was suggested that the Nrf2/Sirt3 pathway was pertinent for the impact of IGF-1 on mitophagy. A perspicuous regulator of mitophagy is PINK1 that obliterates suppressed mitophagy and inhibited IGF-1-induced anti-aging influences in decrepit smooth muscle cells as characteristic of mitophagy in the impact of IGF-1 in cellular senescence [50]. It is perspicuous that IGF-1 constrains cellular senescence or aging through Nrf2/Sirt3-dependent mitophagy activation. Ostensibly, activating IGF-1 signaling constitutes a prospective and newfangled modality to induce mitophagy and decelerate aging or cellular senescence in diabetes mellitus and its sequelae.

Conclusion

Aging, cellular senescence, diabetes and numerous age-related disorders constitute challenges which feature normal, physiologic, chronological aging and clinicopathological aging, premature senescence. Persons in excess of the sixth decade of life are more prpne to the burden inextricably connected with healthy and pathological aging in diabetes. The main objective of individuals and society is the promotion and sustenance of the quality of life that is commensurate with healthy aging and healthspan. An overview of this article has attempted to enunciate parameters, factors, and trajectories which may be tenable for sustainable care and management of aging, diabetes and its complications.

The multifactorial origin of aging, cellular senescence and diabetes with diabetes complications is not well-established. The levels and trajectories of putative risk factors are changing in countries and regions all over the world. Elucidating the encompassing impacts of these changes on present and future generations on present and future trends in aging and diabetes is crucial in counteracting the unhealthy attributes of these diseases.

Bibliography

1. Palmer, A. K., Tchkonia, T., LeBrasseur, N. K., Chini, E. N,, Xu, M. & Kirkland, J. L. (2015). Cellular senescence in type 2 diabetes: A therapeutic opportunity. *Diabetes, 64*(7), 2289-2298.

2. Herrera, M. D., Mingorance, C., Rodriguez-Rodriguez, R. & Alvarez de Sotomayor, M. (2010). Endothelial dysfunction and aging: an update. *Aging Res Rev., 9*(2), 142-152.

3. Prattichizzo, F., De Nigris, V., La Sala, L., Procopio, A. D., Olivieri, F. & Ceriello, A. (2016). "Inflammaging" as a druggable target: A senescence-associated secretory phenotype-centred view of type 2 diabetes. *Oxidative Medicine and Cellular Longevity, 2016*(1810327), 1-10.

4. Mchugh, D. & Gil, J. (2018). Senescence and aging: causes, consequences and therapeutic avenues. *J Cell Biol., 217*(1), 65-77.

5. Chukwuma Sr, C. (2014). Is diabetes a model for gene-environment interaction in premature senescence? *JBAH., 4*(25).

6. Wild, S., Roglic, G., Green, A., Sicree, A. & King, H. (2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care, 27*(5), 1047-1053.

7. Morley, J. E. (2018). Diabetes, sarcopenia, and frailty. *Clin Geriatr Med., 24,* 455-469.

8. Chukwuma Sr, C. (2020). An overview of the neurological consequences of obesity and diabetes. *Journal of Neuroscience and Neuropsychology, 3,* 106.

9. Palmer, A. K., Gustafson, B., Kirkland, J. L. & Smith, U. (2019). Cellular senescence at the nexus between ageing and diabetes. *Diabetologia, 62*(10), 1835-1841.

10. Weir, S. B. (2019). Pancreatic beta-cell ageing: Novel mechanisms and consequences in the management of diabetes. *Endocrine Abstracts.,* 63 PL3.

11. Barinda, A. J., Ikeda, K., Nugrolo, D. B., Wardhana, D. A., Sasaki, N., Honda, S., *et al.* (2020). Endothelial progeria induce adipose tissue senescence and impairs insulin sensitivity through senescence associated secretory phenotype. *Nature Communications, 481,* 11.

12. Huy, H., Sing, H. Y., Kim, M. J., Kim, W. S., *et al.* (2018). TXNIP regulates ALT-mediated cellular senescence by direct interaction under glucose-mediated metabolic stress. *Aging Cell, 17*(6), e12836.

13. Kakoki, M., Sullivan, K. A., Backus, C., Hayes, J. M., Oh, S. S., Hua, K., *et al.* (2010). Lack of both bradykinin B1 and B2 receptors enhances nephropathy, renopathy, and bone mineral loss in Akita diabetic mice. *Proc Nat Acad Sci (USA)., 107*(22), 10190-10195.

14. Li, N., Liu, F., Yang, P., Xiong, F., Yu, Q., Li, J., *et al.* (2019). Aging and stress induced B-cell senescence and its implication in diabetes development. *Ageing(Albany NY), 11*(21), 9947-9959.

15. Shekari, H., Lemmens, K., Gevaert, A. B., De Meyer, G. R. Y. & Segers, V. F. M. (2018). Cellular senescence links aging and diabetes in cardivascular disease. 2018

16. Crochemore, C., Molin, C. F., Montagne, B., Salles, A. & Riachetti, M. (2019). CSB promotes downregulation via histone H3 hypoacetylation is an early determinant of replicative senescence. *Nature Communications, 10,* 1.

17. Bilici, M., Arpaci, D. K., Ilikhan, S. U., Corakci, B. D., Bayraktaroglu, T., Arasli, M., Tekin, I. O. (2017). Type 2 diabetes mellitus associated with premature aging. *Iranian Red Crescent Medical Journal, 19*(6), e14024.

18. Salminen, A. (2020). Activation of immunosuppressive network in the aging process. *Ageing Res Rev., 57,* 100998.

19. Markowski, D. N., Thies, H. W., Guttlieb, A., Wenk, H., Wischnewsky, M. & Bullerdiek, J. (2013). HMGA2 expression in white adipose tissue linking cellular senescence with diabetes. *Genes Nutr., 8,* 449-456.

20. Rosso, A., Balsamo, A., Gambino, R., Dentelli, P., Falcioni, R., Cassader, M., Pegoraro, L., *et al.* (2006). p53 mediates the accelerated onset of senescence of endothelial progenitor cells in diabetes. *JBC., 281,* 4339-4347.

21. Sabbatinelli, J., Prattichizzo, F., Olivieri, F., Procapio, A. D., Rippo, M. R. & Giuliani, A. (2019). Where metabolism meets senescence: focus on endothelial cells. *Front Physiol.* 2019.

22. Castro-Portuguez, R., Sutphin, G. I. (2020). Kynurenine pathway, NAD+ synthesis, and mitochondrial function: Targeting tryptophan metabolism to promote longevity and healthspan. *Exp Geront., 16,* 110841.

23. Testa, R. & Cerriello, A. (2007). Pathogenetic loop between diabetes and cell senescence. *Diabetes Care, 30*(11), 2974-2975.

24. Xiong, Y. & Zhou, L. (2019). The signaling of cellular senescence in diabetic nephropathy. *Oxidative Medicine and Cellular Longevity, 2019*(7495629), 16.

25. Chukwuma Sr, C. (1995). Type II diabetic nephropathy in perspective. *J Diabetes & its Complications., 9*(1), 55-67.

26. Lamoke, F., Shaw, S., Yuan, J., Ananth, S., Duncan, M., Martin, P. & Bartoli, M. (2015). Increased oxidative stress and nitrative stress accelerates aging of the retinal vasculature in the diabetic retina. *PLoS One., 10*(10), e0139664.

27. Chukwuma Sr, C. & Tuomilehto, J. (1993). Diabetes and the risk of stroke. *J Diabetes & Its Complications., 7*(4), 250-262.

28. Vauzour, D., Camprubi-Robles, M., Miquel-Kergoat, S., Andres-Lacueva, C., Barberger-Gateau, P., Bowman, G. L., *et al.* (2017). Nutrition for the ageing brain: towards evidence for an optimal diet. *Ageing Res Rev., 35,* 222-240.

29. Luo, J., Mills, K., le Cessie, S., Noordam, R. & van Heemst, D. (2020). Ageing, age-related diseases and oxidative stress. What to do next? *Ageing Res Rev., 57,* 100982.

30. Chukwuma Sr, C. & Tuomilehto, J. (1998). The 'thrifty' hypotheses: clinical and epidemiological significance for non-insulin dependent diabetes mellitus and cardiovascular disease risk factors. *Euro J Cardiovascular Rehab., 5*(1), 11-23.

31. Mattson, M. P., Longo, V. D. & Harvie, M. (2017). Impact of intermittent fasting on health and disease processes. *Ageing Res Rev., 39,* 46-58.

32. de Cabo, R. & Mattson, M. P. (2019). Effects of intermittent fasting on health, aging and disease. *N Engl J Med., 381,* 2541-2551.

33. Martins, I. J. & Calderon, A. M. (2016). Diet and nutrition reverse Type 3 diabetes and accelerates aging linked to global chronic diseases. *J Dis Res Ther., 2*(2).

34. Basisty, M., Kale, A., Jenn, O. K., Kuehnemann, C., Payne, T., Rao, C., *et al.* (2020). A proteomic atlas of senescence-associated secretomes for aging biomarker development. *PLoS Biol., 18*(1), e3000599.

35. Hrikson, L. J., Prata, L. G. P. L., Bobart, S. A., Evans, T. K., Giorgadze, N., Hashmi, S. K., *et al.* (2019). Senolytics decrease senescent cells in humans: Preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease. *E Bio Medicine., 47,* 446-456.

36. Ji, T., Zhang, X., Xin, Z., Xu, B., Jin, Z., Wu, J., Hu, W. & Yang, Y. (2020). Does perturbation in the mitochondrial protein folding pave the way for neurodegenerative diseases? *Ageing Res Rev., 57,* 100997.

37. Thompson, P. J., Shah, A., Ntranos, V., Van Gool, F., Atkinson, M., Bhushan, A., *et al.* (2019). Targeted elimination of senescent beta cells prevents type 1 diabetes. *Cell Metab., 29*(5), 1045-1060.

38. Ray, B. (2019). Senescent beta cells. *Science, 364*(6446), 1147-1148.

39. Andrenacci, D., Cavaliere, V. & Lattanzi, G. (2020). The role of transposable elements activity in ageing and their possible involvement in laminopathic diseases. *Ageing Res Rev., 57,* 100995.

40. Cardoso, A. L., Fernandes, A., Aguilar-Pimental, J. A., de Angelis, M. H., Guedes, J. R., Brito, M. A. Ortolano, S., *et al.* (2018). Towards frailty biomarkers: Candidates from genes and pathways regulated in aging and age-related diseases. *Ageing Res Rev., 47,* 214-217.

41. Yang, P., Perlmutter, J. S., Benzinger, T. L. S., Morris, J. C. & Xu, J. (2020). Dopamine D3 receptor: A neglected participant in Parkinson disease pathogenesis and treatment? *Ageing Res Rev., 57,* 100994.

42. 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., 2018*(3).

43. Longo, M., Bellastella, G., Malorino, M. I., Meier, J. J., Esposito, K. & Guigliano, D. (2019). Diabetes and aging: From treatment goals to pharmacologic therapy. *Front Endocrinol.*

44. Chukwuma Sr, C. (2020). Ecological attributes between the association of mortality and putative risk factors of cardiovascular disease. *IJCBR., 6*(3), 18-23

45. Chukwuma Sr, C. (2020). Ecological features of the association between mortality and determinants or salient risk factors of cardiovascular disease. *Int J Clin Biomed Res., 6*(3), 18-23.

46. Zhavorosikov, A., Mamoshina, P., Vanhaelen, Q., Scheibye-Knudsen, M., Moskalev, A. & Aliper, A. (2019). Artificial intelligence for aging and longevity research: Recent advances and perspectives. *Ageing Res Rev., 49,* 49-66.

47. Boyle, J. P., Thompson, T. J., Gregg, E. W., Barker, L. E. & Williamson, D. F. (2010). Projections of the year 2050 burden of diabetes in the US adult population: dynamic modelling of incidence, mortality, and prediabetes prevalence. *Popul Health Metr., 8,* 29.

48. Chukwuma Sr, C. (1993). Type 1 diabetic nephropathy: clinical characteristics and economic impact. *J Diabetes & Its Complications., 7*(1), 15-27.

49. Spinelli, R., Parrillo, L., Longo, M., Florese, P., Desiderio, A., Zatterale, F., *et al.* (2020). Metabolic basis of aging in chronic metabolic diseases. *J Endocrinol Invest., 43,* 1373-1389.

50. Hou, X., Li, Z., Higashi, Y., Delafontaine, P. & Sukhanov, S. (2020). Insulin-like growth factor 1 prevents cellular aging via activation of mitophagy. *Journal of Aging Research.,* 4939.