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Is Diabetes a Model for Gene-environment Interaction in Premature Senescence?

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Abstract
A vast majority of human diseases or disorders are invariably associated with the complex regulations and functions of genes. These also involved in the integration of environmental signals for cells to modulate the functional output of the genome. The ageing process reflects the overall presentation of an organism and the interaction of its genes with the environment. Ageing results from a plethora of processes, which potentially include factors such as diabetes, immune system decline, oxidative damage, rates of apoptosis, and telomere shortening. Persons detected with shorter telomere lengths usually present with accelerated biological ageing, especially those with diabetes mellitus, glucose intolerance, and hypertension. Adverse social factors may be contributory to a worse prognosis for subjects with diabetes mellitus as regards early ageing.The deduction is that diabetes is inextricably linked with "premature ageing". There is appreciable variation in the rate of progression of ageing in humans. A simple biological model may not be sufficient to observe both the clinical and theoretical modalities to understand the mechanisms of gene-environment interaction for diabetes mellitus and premature ageing. The potential clinical and gerontological implications of this study are to configure the population at risk for developing premature ageing among diabetic patients in order to develop early therapeutic strategies and curtail financial costs to prevent untoward sequelae.
Keywords: Diabetes; model; gene; environment; premature ageing; senescence, therapy, costs.

1. INTRODUCTION

The accelerated ageing disorders or diseases such as type 2 diabetes, cancer, atherosclerosis and cardiovascular are essentially genetic perturbations which exacerbate exponentially with increased lifespan. Ageing or senescence increases susceptibility to age-related diseases, whereas genetics is a determinant of susceptibility or resistance in intra- or inter-species relationship.The world wide prevalence of diabetes has now reached epidemic dimensions; with the prevalence of type 2 diabetes (T2D) becoming twice greater in the last three decades as it increases in a geometric rate. In 2010, the estimate of presenting diabetes was 6.4% of the global adult population, that is, 285 million [1,2]. Currently, the T2D incidence has been on a steady increase in the younger population. Diabetes is now very well associated with ageing. The associated health and financial burdens, challenges and constraints are expansive. The common forms of T2D present multifactorial aetiologies with involvement of intricate interactions of genetic, epigenetic and environmental attributes. The preponderant role of the environment, especially diet and sedentary lifestyles, in the risk of diabetes is the importance of accelerating prevalence of early onset T2D or prediabetic features or perturbations in young people, particularly children. Presently, the role of early life environment in programming or priming diabetes risk has been elucidated in several human and animal studies. In perspective, there has been a linkage between low birthweight, a proxy for suboptimal in utero growth, and diabetes risk in the adult. Diverse expositions, such as maternal obesity, and/or maternal diabetes may significantly impact on the health and outcomes of the offspring. It is pertinent for the underlying processes to be configured in order to prevent, retard or reverse a primed or programmed risk for T2D influenced by pre- and/or postnatal environmental attributes as to have improved health outcomes and ameliorate premature metabolic perturbation that would culminate in premature senescence [2].

A vast majority of human diseases or disorders are invariably associated with the complex regulations and functions of genes. These also involved in the integration of environmental signals for cells to modulate the functional output of the genome. T2D is due to the interaction of a genetic predisposition, behavioural and environmental factors. T2D represented a “thrifty genotype” [3] that had a selective advantage in primitive periods. Persons who were “metabolically thrifty” and capable to harness and store an enhanced concentration of energy as fat in times of food abundance were more likely to survive famine. A vast majority of the global population rely on an incessant supply of calorie-dense processed foods combined with decreased physical activity resulting in elevated proportions of T2D prevalence. The main environmental risk factors for T2D are general obesity, body fat distribution [estimated by waist-to-hip circumference ratio, WHR, and intrauterine environment [3].

T2D is associated with the chronic increase of blood glucose concentrations combined with cellular resistance to the insulin hormone. How could such perturbations in glucose/insulin metabolism culminate in chronic disorders

related with ageing? In ageing, as in diabetes mellitus, the increase in the levels of glucose and other reducing sugars secondary to age-induced insulin resistance can react non-enzymatically with proteins and nucleic acids to develop into substances which degenerate tissue elasticity. Also, disturbances in glucose/insulin metabolism are related with enhanced lipid peroxidation secondary to expansive free radical formation [4]. Fat tissue secretes multiple metabolic active factors, which are potentially responsible for insulin resistance to be developed. Therefore, manipulation of diet that effect the glucose/insulin system may elongate lifespan favourably and decrease the incidence of chronic diseases associated with ageing.

Albeit, the peak age at onset of T1D is at puberty, T1D invariably emanates in adulthood with no significant gender disparities in incidence among persons diagnosed before the age of 15 years [5]. The recent temporal increase in T1D incidence depicts an alteration in the global environment than variation in the gene population that goes through a litany of generations. Research has focused more on viruses and infant nutrition as the environmental rick factors for T1D.

This paper focuses on findings of diverse terms of application to explicate further the mechanisms of gene-environment interactions in diabetes, probably as a model in premature senescence.

2. THE PARAMETERS OF AGEING AS RELATED TO DISEASES

Ageing reflects the overall presentation of the genotype of an organism and the interaction of these genes with the internal and external milieu. Ageing portends a risk of evolving age-related perturbations such as diabetes mellitus, cardiovascular disease, cancer, dementia, and other degenerative disorders, which eventually culminate in death. Type 2 diabetes is believed to be inextricably linked with both an environmental component and genetic aetiologies. A simple biological model of ageing is well-nigh impossible due to the expansive complexity of organisms. However, such a model may be useful as a trajectory to observe both the clinical and theoretical modalities as links to understand the mechanisms of gene-environment interaction for diabetes mellitus and early senescence.

Ageing is characterised as biological and chronological age. Chronological age is a fixed dimension based on the calendar, whereas biological age depicts inter-individual variation in growth and ageing [6]. Biological gerontology emphasises the dimension of average ageing, whereas less focus has been on the individual differences on the rates of ageing. The aim of ageing research is the prevention or postponement of the debilitative physical alterations in old age. In normal ageing, there is usual ageing in which the extrinsic factors highlight the effects of ageing alone; and successful ageing with extrinsic factors playing a neutral or positive role. In unsuccessful ageing, age-related diseases proceed faster or commence earlier than in successful ageing. The clinical manifestations of these diseases are more aggravated and expressed at a younger (chronological) age, resulting in premature morbidity and mortality [6]. Unsuccessful ageing is thus regarded as a process of early onset ageing or accelerated ageing, and could be limited to one organ system, progress in isolation in some organ systems, or have a uniform process in the entire body.

The major heterogeneity within age groups has been either neglected or associated with variations in genetic attributes. This perspective fails to take into cognizance the crucial aspect of intrinsic factors and how psychosocial and physiologic variables interact, as well as the heterogeneity within different age groups. Individuals ageing successfully would exhibit little or no age deterioration in physiologic function, while those ageing "usually" would present with disease-related derangements, described as the effects of ageing. The distinctive strong association between diabetes and unsuccessful ageing is remarkable, probably reflecting the higher prevalence of diverse complications among diabetic individuals.

3. MAJOR FACTORS IN THE GENE-ENVIRONMENT ASPECTS OF PREMATURE AGEING

Longevity scientists use the tools of genomics for the generation of a molecular fingerprint of ageing and the development of interventions which retard or reverse the ageing process. The genotype of an individual will affect the rate at which an individual ages. Gerontogenes regulate the rates of ageing in certain organisms, but not in humans [6]. There are numerous natural and synthetic genotoxins, plants and fungi which contribute as sources for DNA or chromosome derangement. Since these toxins are perturbative to genetic material, they may effect on ageing. It is established that cellular ageing contributes to organismal ageing, but the extent to which organismal ageing is caused by cellular ageing remains to be established. Age-related diseases are frequently viewed as distinct pathologies instead of as an inevitable aspect of "normal" ageing.

Studies of premature ageing have identified a defect or a mutant allele of the WRN gene responsible for where persons at a young (chronological age) develop certain features associated with ageing. Signs of defective DNA

metabolism have been identified in cells obtained from WS patients with defective WRN gene identifiable with the deposition of deranged DNA in cells resulting in premature development of age-related disorders [7].

From cultured human fibroblasts, to elucidate the biology of ageing and the origins of age-dependent diseases indicated that the replicative lifespan of cultures was inversely proportional to the chronological age of the tissue donor, and cultures obtained from persons with two inherited disorders of premature ageing, progeria, and Werner's syndrome (WS], presented with more debilitative growth capacity. The aetiology of the accelerated ageing is not clear, however, genomic instability that is a strong characteristic of WS may be implicated. A correlation between accelerated senescence and WS ageing in vivo depicts that these kinase inhibitors could be the basis of antiageing therapies for patients with WS [8].

It is suggested that the several longevity- and disease-related genes in humans exert their impact by genetic control over cell division (9]. A vast majority of cells have a finite life span, that is, following a specific number of divisions, a state is reached with the possibility of no more division. The synthetic ability of DNA is impeded, with failure to function appropriately. This "replicative senescence" may explain certain aspects of the ageing process. Analysis of replicative senescence reveals that cell division is accompanied by the reduction of telomere lengths. Due to the long lifespan of humans and the representative short telomeres, attrition in telomere length may be the main determinant of human ageing both at the cellular and organ levels as well as perhaps the systemic level in diabetic subjects. Telomere replication is both cell cycle- and developmentally regulated, with a probable complex control mechanism. The pace of this biological clock fluctuates, while telomere attrition is vastly dependent on oxidative stress/antioxidant defence [9]. Increased glucose levels, typical of diabetic hyperglycaemia, induces oxidative DNA degradation, augmented telomere attrition and human vascular endothelial cell senescence in vitro. After the advent of chronic oxidative stress, these cells are also vulnerable to aberrant elongation of telomeres resulting in heterogeneity in inter-chromosome telomere DNA length. High glucose-induced DNA degradation leads to human endothelial cell telomere heterogeneity and results in cellular replicative senescence by harnessing DNA repair factors and telomere checkpoint proteins. It is pertinent to definitely establish that genes in animal models mimic or are an exact replica of those found in mammals.

The progression of cellular senescence and ageing has been inextricably linked with degradation of nuclear and mitochondrial DNA (mtDNA). mtDNA is vulnerable to oxidative degradation and is included in the "mitochondrial theory of ageing". mtDNA may be a target for glucose-induced oxidative damage in cultured human endothelial cells; and increased extracellular glucose concentrations promote the generation of reactive oxygen species within mitochondria via augmented metabolism [10].

Increased oxidative stress has a major role in the pathogenesis of diabetic complications, and it is a secondary indicator of end-stage tissue degradation in diabetes mellitus. Increased glycoxidation and lipoxidation products in plasma and tissue proteins indicate that oxidative stress is augmented in diabetes. Elevated concentrations of oxidizable substrates could also explain the elevation of glycoxidation and lipoxidation products in tissue proteins in the absence of necessarily triggering a rise in oxidative stress. The augmented chemical modification of proteins by carbohydrates and lipids in diabetes mellitus is a resultant effect of overload of metabolic pathways associated with detoxification of reactive carbonyl species, culminating in an overall increase in steady-state levels of reactive carbonyls generated by both oxidative and nonoxidative reactions [11].

The molecular mechanisms involved in the premature senescence process associated with hyperglycaemia include oxidative stress, telomere shortening, decreased DNA repair capacity, and protein glycation resulting in the formation of advanced glycosylation endproducts (AGEs) [12]. AGEs apparently toughen or stiffen tissues, and are involved in several age-related conditions. Cross-linking is a special focus of research also on diabetes, a disorder in which complications mimic physiologic alterations that can accompany advancing age. The reaction between blood glucose and protein is reversible resulting in a non-toxic glycated protein. With the accumulation of glycated proteins a non-reversible rearrangement or Maillard reaction occurs that presents little or no toxicity but do form interlinked cross bridges and with other substances to form non-reactive and potentially toxic AGEs. With increased blood glucose levels, there is an increase in the production of AGEs. The increase of blood glucose levels is at a rate of 1-2% per decade with ageing. Immune cells called macrophages are able to hinder glycation; but this process is incomplete and the cross-link proteins (AGEs) accumulate with age.

4. SEX AND AGE DISPARITIES ASSOCIATED WITH TELOMERE LENGTH

An investigation of human telomere length disparities on single chromosome arms of persons in disparate age groups and sexes showed that during ageing, telomeres gradually decrease in length, with eventual culmination in cellular senescence. Male subjects presented with shorter telomere and higher attrition rates. Each

chromosome arm had its age-specific telomere length and attrition pattern, culminating in heterogeneity in chromosome-specific regression lines. This disparate erosion pattern may be predetermined due to the correlation between average telomere length of single chromosome arms in newborns and their annual attrition rate. In addition to sex-specific disparities, chromosome arm-specific telomere lengths were overtly identical in both men and women with the implication that chromosome arm specifically regulates telomere length independent of gender, resulting in interchromosomal telomere variations [13].

The longetivity gender gap is extremely complicated and may develop from sex-related hormonal disparities and from somatic cell selection that are susceptible to cells more resistant to exposures over time. Animal and human research showed higher telomerase activity [14] and longer telomeres in female subjects compared to male subjects, with estrogens contributing to the gender disparities. The cardioprotective effects of estrogens through indirect mechanisms on lipoprotein metabolism and by direct effects on vascular endothelial cells and smooth muscle cells could contribute to the decreased incidence of cardiovascular disease detected in premenopausal women and not in men [15]. Also, estrogens could contribute to longer telomeres in women compared with age-matched men, thus correlating with decreased incidence of cardiovascular disorders in premenopausal women [16].

In twin pairs involving both sexes of different age groups, TRF length in WBCs correlated with diastolic blood pressure but not with systolic blood pressure, indicating a negative association between TRF length and pulse pressure. The correlation between telomere length and pulse pressure was independent of gender with high apparent heritability as regards both parameters. Investigation of WBC telomere length and pulse pressure parameters which are associated with large artery stiffness – pulse pressure and pulse wave velocity [15] on subjects of different age groups and sexes not on antihypertensive drugs, showed negative correlation of telomere length with age in both sexes, and multivariate analysis showed that telomere shortening was significantly associated with elevated pulse pressure and pulse wave velocity only in men. Both studies revealed age-adjusted longer telomeres in women, implying that biological ageing is more advanced in male persons than in female persons [17]. Also, estrogens could contribute to longer telomeres in women compared with age-matched men, thus correlating with decreased incidence of cardiovascular disorders in premenopausal women.

The issue is whether telomere length, as a possible biomarker of biological ageing provides a more reliable feature than chronological age for variation in arterial stiffness, assessed by the measurement of pulse pressure and aortic pulse wave velocity [17]. Telomere length makes provision of an increased possibility to chronological age of variations in pulse pressure and pulse wave velocity among men, such that men presenting with shorter telomere length have greater possibility of having high pulse pressure and pulse wave velocity, which are indicative of large artery stiffness; whereas women had longer telomere lengths suggesting that for a given chronological age, the biological ageing of men is higher than that of women. Symptoms are not evident until endothelial/vascular dysfunction is realised, therefore, a simple and sensitive early diagnostic method such as pulse wave velocity requires to be developed for prevention and medical treatment in diabetic patients. A high concordance of TRF length observed between mothers and offsprings as well as between fathers and daughters (but not between fathers and sons and between spouses) is X-linked mechanism of inheritance [18].

5. ENVIRONMENTAL FACTORS IN EARLY DEVELOPMENT

It is perspicuous that there are mechanisms related to foetal programming in a multi-dimensional setting, with the comparison of early life growth and longevity patterns within generations. Low rates of growth in early life are associated with an elevation of age-related disease in later life. Early development of living organisms leads to a remarkable high initial damage load (HIDL), that is comparable with the extent of subsequent ageing-related degradation accumulating in the rest of adult life [19]. This HIDL hypothesis was tested and established in humans that familial transmission of lifespan from parents to their children takes a non-linear accelerating trajectory, with steeper slopes for the lifespan of offspring of longer lived parents. Thus, increasing evidence is extant to support the foetal origins of adult degenerative disorders, and early-life programming of ageing and longevity. The HIDL hypothesis predicts that even small progress to optimise the early developmental processes can potentially culminate in a formidable prevention of numerous diseases in later life to postpone age-related morbidity and mortality, as well as significant prolongation of healthy lifespan.

Undernutrition and decreased growth in utero as well as during infancy result in more accelerated ageing in some systems. Several age-related diseases are associated with inadequate growth and under-nourishment in early life, and there may be an interaction of genetic factors with growth and nutritional influences to determine musculo-skeletal ageing in later life (20). It is perspicuous that under-nutrition and poor growth in foetal or early life may shorten longevity, while a post-weaning caloric restriction actually prolongs life. Caloric restriction

(CR) is a dietary regime, low in calories without undernutrition. CR has been found to extend the lifespan of several organisms [21]. Even though, it was suggested that CR works by decreasing the concentrations of reactive oxygen species during respiration, the lifespan mechanism remains polemic.

Moreover, foetal programming and decreased foetal growth may be significant for the risk to develop insulin resistance and T2D with the implication that the ageing process may be influenced to programming in early life. It is not yet clear, however, if retardation of foetal or early life growth is influenced more by genetic or environmental factors in the pregnant woman. T2D is associated with low birthweight accompanied by obesity in adulthood. Individuals with the disorder may present with a peculiar pattern of growth from birth through childhood. It is suggested that T2D is programmed in utero with concomitant low rates of foetal growth [22].

The early-life period is a critical stage of development, and influences within this period may challenge the metabolic status of the adult. The role of maternal and in utero impacts on the developmental precipitating of T2D risk in both human epidemiological studies and experimental animal models to demonstrate that early dietary experience are liable to exacerbate the onset of age-related metabolic perturbations and insulin resistance as well as T2D, obesity, hypertension and cardiovascular derangements. It is suggested that impaired maternal nutrition precipitates a prediabetes phenotype, as frequently exhibited as insulin resistance in early stages of life. Therefore, maternal diet constitutes a critical determinant of premature T2D risk. Although, the processes which link early nutrition with age-related metabolic decrease are not clear, it may be that dysfunctions in a number of mechanisms are inextricably linked in cellular aging, such as alterations in longevity-associated Sirtuin activity, epigenetic regulation of specific metabolic genes, and mitochondrial perturbation. Pharmacological interactions in utero and dietary supplements during early postnatal life may mitigate insulin resistance and decrease T2D risk. Further studies may demonstrate the relationship between the early environment and prolonged impacts on metabolism. These will strategically augment the interventions which will prevent or ameliorate metabolic decline and the premature onset ofT2D in present and future generations [1]

6. MODALITIES TO CURTAIL COSTS AND PREVENT THE PREMATURE SENESCENCE ASSOCIATED WITH DIABETES

Aging or senescence constitutes the major risk factor for several chronic diseases, disabilities and decrease in health status [23, 24]. Comorbidity, complications and geriatric perturbations influence diabetes care including financial constraints in medical and healthcare modalities for the treatment of older adults with diabetes. Expansive public health programmes do help; but effective and efficient interventions, surveillance, research, better and improved policies need to be put in place for the accelerating diabetes burden among older adults [25]. Senescent cells have been identified as potential therapeutic targets to treat ageing and age-related disorders [23]. There are demonstrated human and animal experiments to slow or prevent premature ageing associated with diabetes. Given that vascular disease is accepted as an indicator of pathological ageing superimposed on normal vascular ageing, it could be stipulated that with current belief that the control of hyperglycaemia can successfully prevent microvascular, but not macrovascular perturbations. The combined efforts in the treatment of the entire CV risk factors [26] at the same time, for instance, hypertension and hyperglycaemia may be a success in obviating macrovascular disease and its manifestations instead of the sole treatment of a single risk factor.

A study [27] demonstrated that a decreased number of circulating endothelial progenitor cells (EPCs) are involved in cardiovascular diabetes complication. In diabetic mice, the absence of adiponectin exacerbated the hyperglycaemia-induced reduction in circulating EPCs, and also mitigated the stimulatory influences on the production of EPCs, and re-endotheliazation. Treatment with adiponectin prevented elevated glucose-induced premature senescence. At the molecular level, adiponectin reduced elevated glucose-induced aggregation of intracellular reactive oxygen species and eventually suppressed activation and expression of the senescent marker [27]. The protective influences of adiponectin on vascular complications of diabetes are suggested to be partly in its capability to counteract hyperglycaemia-mediated reduction in the number of circulating EPCs.

It was found that elevated glucose-induced oxidative stress exacerbated premature stress-induced senescence in young rat AF cells in a dose- and time-dependent feature other than replicative senescence [28]. It is suggested that prevention of augmented oxidative stress using strict blood glucose control is vital to ameliorate, retard or prevent premature intervertebral disc degeneration in young patients presenting with diabetes.

Another study [29] showed that age-related reduction of beta-cell mass is marginal following maturation, and the decrease of beta-cell mass may be a specific process in diabetes. The effect of BMI on the islet cell structure is restricted in Japanese pressenting normal glucose tolerance. Islet density was elevated in the young, but decreased after maturation.

It is understandable that most medical and health personnel agree that ageing is an independent risk factor for human atherosclerosis, while atherosclerosis is accepted as a feature of aging in humans by numerous gerontologists. Increased calorie intake predisposes to diabetes and hyperinsulinaemia; in contrast, dysregulation of the insulin pathway has been demonstrated to induce cellular senescence in vitro [30]. Caloric restriction or decreased insulin signals promote the lifespan of various species and reduces biomarkers of cellular senescence in vivo. It is evident that cellular senescence contributes to the pathogenesis of human atherosclerosis. Senescent vascular cells are accumulated in human atheroma tissues and reveal diverse characteristics of derangements [30].

Also, the senescent cardiac phenotype is associated with alterations in mitochondrial function and biogenesis resulting in perturbations in the provision of energy. The association between myocardial senescence and Pim kinases is pertinent as Pim 1-kinase is partly cardioprotective in the maintenance of mitochondrial integrity [31]. Thus, myocardial senescence may be enhanced by dissipation of Pim resulting in premature ageing and aberrant mitochondrial function. Pim kinases prevent cardiac senescence and preserve healthy mitochondria with resultant efficient cellular energetic attributes [31]. Furthermore, clinical data depict that metformin that is a hypoglycaemic agent acts as an endothelial protective substance [32]. Hyperglycaemia-induced down-regulation of SIRTI was significant in diabetes-induced endothelial senescence. The protective action of metformin on hyperglycaemia-induced endothelial dysfunction was due in part to the effects on the expression and/or activity of SIRTI [32].

7. DISCUSSION

Ageing constitutes a principal biomedical challenge. Genes do regulate the process of ageing; although, the environment is also significant. In essence, the biomedical/biochemical processes are influenced by numerous genes which interact with the environment as they affect normal ageing. As the disease burden of ageing will invariably overwhelm the healthcare system in the coming decades, it is significant to have an expansive understanding of biological ageing as it relates to the presenting disease. The development of age-related diseases depict at varied rates in a specific individual. Subjects with diabetes mellitus seemed to age more prematurely than non-diabetic or healthy individuals. It is universally accepted that the rate of ageing is determined both genetically and environmentally. Definitely, no single factor can be indicted for the ageing process. Diabetes mellitus is frequently related to premature senescence syndrome [1, 2,10 ,16].

Cellular ageing may potentiate the mechanisms which are associated in reducing myocardial contractility in diabetes and; diabetes associated with senescence may augment the risk to develop prmature ageing. The modulation of telomere activity and telomere length, with the mitigation of the formation of reactive oxygen species are crucial novel targets for developing therapeutic roles to prevent premature ageing. Increasing reduction in telomere length has been indicated in several diseases including T2D. These depicted that the shortening of telomere length increases as diabetes progresses. The detection time of progression is suggestive that there exists a simultaneous corresponding acceleration of inflammation and/or oxidative stress that relates directly with telomere shortening [33]. Although, reduced telomere length are related to several risk factors of diabetes, there is emphasis on the clustering of augmented ageing characteristics, such as shortened telomeres, decreased mtDNa levels, hypoadiponectinemia, decreased HDL, and high oxidative stress in T2D patients [34]. Insulin receptor signaling has revealed that down regulation of insulin receptor signaling via CR augments the life span in mice [35].

Hyperglycaemia as a common denominator and hallmark of the different states of diabetes mellitus is poor metabolic control, and is an internal environmental promoter both of pathophysiological processes culminating in premature senescence and, for example, of gene up-regulation resulting in vascular damage. This process of premature senescence associated with hyperglycaemia is measurable/detectable in numerous organs and are potentially preventable. A support of the latter statement is that a healthy lifestyle has been found to stem the transition from IGT to overt T2D [36], and, therefore, the risk of organ damage from hyperglycaemia. It has been established that the Amadori product, glycated albumin, augments premature cell senescence in mesangial cells by the activation of the insulin growth factor, IGF-1 receptor signaling pathways and the resultant decrease in the antioxidant enzyme catalase [37]. Amadori products are present in debilitative conditions such as, diabetes and ageing; and are invariably associated in diabetic nephropathy or age-related renal dysfunction.

A strong defence against free radicals is the manufacture by the body of antioxidants, which are able to neutralise the oxygen radicals [38], and eliminate the deranging effects. However, animal studies have not yet directly established that the use of natural antioxidants, such as vitamin E lead to the improvement of health or

extend lifespan. Scientists are searching for other avenues to combat oxidative stress, because free radicals constitute just a class of toxins encountered daily. The scientific data undergirding the usage of antioxidants as dietary supplements are mixed, with no evidence that consumption of any currently available antioxidant compound contributes beneficially to the rate of human ageing. It is possible to eventually develop similar compounds to ameliorate oxidative stress in humans and retard or decrease certain age-related disorders [39, 40]. A clear understanding of the up-regulation by hyperglycaemia of genes associated with ageing may provide more latitude to understand the process.

8. CONCLUSION

Expansive studies are required for the evaluation of various markers of glycaemia, and relevant metabolic abnormalities in the ageing of individuals with diabetes mellitus. It is pertinent to investigate mechanisms related to foetal programming in a multi-dimensional setting, with the comparison of early life growth and longevity patterns encompassing generations. WBCs are proliferative cells, which are readily available from humans. These cells have been employed to determine whether telomere dynamics can provide information in addition to chronological age, about vulnerability to disturbances of ageing. Inasmuch as, telomere dynamics may provide information with respect to the biology of ageing, a model linking telomere dynamics, diabetes mellitus, and gene-environment interaction is appreciable. Telomere length decreased in WBCs from T1D patients in comparison to age-matched nondiabetic persons. This parameter was not distinguishable when compared to T2D patients and nondiabetic controls, and was suggested that telomere shortening presents in subsets of WBCs which are involved in the pathogenesis of T1D. Does this suggest that telomere length has no correlation with ageing? The shortened terminal restriction fragment (TRF) length of WBCs of subjects with T1D possibly reflects a significant decrease in the TRF length of subsets of WBCs which are involved in the pathogenesis of T1D [41].

To assess telomere length is important because telomeres are useful to identify most abnormal cellular phenotypes, determine the efficacy of inhibitors, and provide prognostic information helpful in guiding treatment modalities. Therefore, the methods for measuring telomere length need to be efficient and facilitate the process to determine minute and subtle alterations in telomere length. Obviously, telomere length is a marker of telomerase activity, and its measurement by various methods are of use. The quantitative flow FISH in combination with digital microscopy will enhance efficient large-scale sample processing and analysis of telomere lengths. It is required to determine the efficacy of novel therapeutic regimens directed at the modification of telomere length. Therefore, encompassing and basic research and epidemiological studies are necessary to determine if telomere attrition is an exclusive cardiometabolic risk factor or the resultant effect of age-associated disorders. The rapidity of telomere length shortening may be a surrogate for the chronic oxidative stress [42] and/or inflammation. Accelerated telomere shortening is may be associated with ethnicity [43], gender [44] and lifestyle disorders which are linked to some metabolic factors, for instance, obesity, insulin resistance, hypernutrition and sedentary lifestyle [45].

It has been demonstrated how stress-induced anabolic/catabolic imbalance, expressed partly by elevated cortisol, glucose and insulin as well as decreased androgens and growth hormones may result in oxidative stress and systemic inflammation leading to impairment of cell ageing processes. High intake of energy-enriched food and obesity play a vital mediating role in this trajectory. These cause insulin resistance and the enhancement of energy storage in abdominal fat tissue. This body habitus is related to systemic inflammation and oxidative stress which impact on cell metabolism with resultant acceleration of cellular ageing with possible effect on autophagy, sirtuins and telomere maintenance [46]. Since the ageing process as related to premature cellular senescence is a multifactorial and extremely variable entity that causes several dysfunctional states in tissues, the application of telomere length gives new and ample opportunity for research into metabolic and cardiovascular anomalies, especially diabetes mellitus. An investigation in the relatedness between genetic polymorphisms with functional impacts on redox regulation in subjects with T2D, that after adjustment for age, gender, smoking, BMI, diabetes duration and lipid parameters, the carriers of GSTM1/GSST1-null haplotype depicted an augmented risk for myocardial infarction [47]. It is suggested that GSTM1/GSTT1 haplotype is a genetic risk factor for myocardial infarction in patients with T2D.

The increased rate of changes in glucose regulation in adults may be due to a complex set of risk factors which contribute to augmentation of insulin resistance with ageing and deranged pancreatic islet cell function [48]. The age-associated insulin resistance is principally due to lifestyle factors; and, therefore, improvement in diet and exercise may be useful in preventing progression to diabetes and premature senescence. Also, there exist age-associated declines of pancreatic islet function and possible proliferative capacity resulting from both ageing effects on the islets and genetic factors [49]. Although, sustainable parameters in lifestyle may retard age-

associated hyperglycaemia partly by decreasing demand on extant beta cells, it is possible that several other adults will eventually succumb to diabetes until there are viable interventions to delay or eliminate the effects of ageing on pancreatic islet function, as an attribute for the management of hyperglycaemia in persons with type 2 diabetes [3, 49].

Cells do regulate the ageing process, and the environment playa a vital role resulting in early onset rather than normal ageing in diseases such as diabetes. The ageing process as determined by gene-environment interactions are unaltered with age-related diseases (46) or disorders such as insulin resistance and diabetes. The ageing process reflects the overall presentation of an organism and the interaction of its genes with the environment. Ageing results from a plethora of processes, which potentially include factors such as diabetes, immune system decline, oxidative damage, rates of apoptosis, and telomere shortening. The potential clinical and gerontological implications of this study are to configure the population at risk for developing premature ageing among diabetic patients in order to develop early therapeutic strategies to prevent untoward sequelae. Diabetes mellitus associated to premature aging may increase the risk of developing a cardiomyopathy. Thus, the modulation of telomerase activity and the control of telomere length, as well as the amelioration of the formation of reactive oxygen species could form valuable new targets to develop therapeutic tools to prevent diabetic complications resulting in premature senescence. Early life development and lifestyle also affect the ageing process. Calorie restriction may be of therapeutic value as used currently as a paradigm to develop substances which promote and extend life. There must be expansive interventions (50) to mitigate the impacts of the metabolic syndrome and type 2 diabetes. It is, therefore, clear that diabetes is inextricably linked with "premature ageing". There is appreciable variation in the rate of progression of ageing in humans. A simple biological model may not be sufficient to observe both the clinical and theoretical modalities to understand the mechanisms of gene-environment interaction for diabetes mellitus and premature ageing.

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