Vitamin D, Oxidative-Stress and Aging

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Recent advances in vitamin D research indicate that this vitamin, a secosteroid hormone, has beneficial effects on several body systems other than the musculoskeletal system. Both 25 dihydroxy vitamin D [25(OH)2D] and its active hormonal form, 1,25-dihydroxyvitamin D [1,25(OH)2D] are essential for human physiological functions, including damping down inflammation and the excessive intracellular oxidative stresses. Vitamin D is one of the key controllers of systemic inflammation, oxidative stress and mitochondrial respiratory function, and thus, the aging process in humans. In turn, molecular and cellular actions form 1,25(OH)2D slow down oxidative stress, cell and tissue damage, and the aging process. On the other hand, hypovitaminosis D impairs mitochondrial functions, and enhances oxidative stress and systemic inflammation. The interaction of 1,25(OH)2D with its intracellular receptors modulates vitamin D–dependent gene transcription and activation of vitamin D-responsive elements, which triggers multiple second messenger systems. Thus, it is not surprising that hypovitaminosis D increases the incidence and severity of several age-related common diseases, such as metabolic disorders that are linked to oxidative stress. These include obesity, insulin resistance, type 2 diabetes, hypertension, pregnancy complications, memory disorders, osteoporosis, autoimmune diseases, certain cancers, and systemic inflammatory diseases. Vitamin D adequacy leads to less oxidative stress and improves mitochondrial and endocrine functions, reducing the risks of disorders, such as autoimmunity, infections, metabolic derangements, and impairment of DNA repair; all of this aids a healthy, graceful aging process. Vitamin D is also a potent anti-oxidant that facilitates balanced mitochondrial activities, preventing oxidative stress-related protein oxidation, lipid peroxidation, and DNA damage. New understandings of vitamin D-related advances in metabolomics, transcriptomics, epigenetics, in relation to its ability to control oxidative stress in conjunction with micronutrients, vitamins, and antioxidants, following normalization of serum 25(OH)D and tissue 1,25(OH)2D concentrations, likely to promise cost-effective better clinical outcomes in humans.

Calcitriol 1,25(OH)2D Diabetes DNA Endocrine Epigenetics Hormones Mitochondria

1. Introduction

Vitamin D affects all systems in the body. Both 25 dihydroxy vitamin D [$25(OH)_2D$] and its active hormonal form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$; calcitriol] are essential for human physiological functions, including damping down inflammation [1] and the excessive intracellular oxidative stresses [2][3][4]. Vitamin D is a potent anti-oxidant that improves mitochondrial activity, preventing oxidative stress-related protein oxidation, lipid peroxidation, and

DNA damage [5]. Recent data support less known, key functions of vitamin D on non-musculoskeletal functions, particularly on mitochondrial respiratory functions/energy generation, oxidative stress, and the aging process [6][7].

2. Role of Calcitriol on Inflammation and Oxidative Stress

Calcitriol dampen inflammation, oxidative stress, cell/tissue damage, and thereby, the aging process. Hypovitaminosis D, on the other hand, accelerates these processes. Consequently, vitamin D deficiency increases the incidence and/or severity of many age-related metabolic disorders that are linked to oxidative stress and accelerates the aging process [8]. Diseases that get worsen by vitamin D inadequacy include, insulin resistance, type 2 diabetes, obesity, hypertension, memory disorders, osteoporosis, certain cancers, and systemic inflammatory diseases, and pregnancy-associated complications [9].

In addition to hypovitaminosis D, toxins, metabolic abnormalities, and the aging process itself causes mitochondrial dysfunction [10][11][12][13][14]. Abnormal mitochondria produce suboptimal amounts of ATP while generating excess ROS; a double whammy, creating a vicious cycle of enhancing the effects from excessive oxidative stress [13][14][15]. Moreover, in the presence of vitamin D deficiency, DNA damage, impair DNA repair systems, premature cell death, and accelerated aging get accelerated [12][16]. Vitamin D deficiency causes mitochondrial dysfunction that is synergized by intracellular inflammation [17][18][19][20].

Adequately powered, properly designed randomized controlled clinical studies in subjects with vitamin D deficiency (i.e., serum 25(OH)D concentrations less than 20 ng/mL) using the nutrient vitamin D as the key intervention and predefined hard endpoints/primary outcomes are still lacking [21]. Protective effects of vitamin D improves mitochondrial and endocrine functions, reducing the risks of autoimmunity, infections, metabolic derangements, and impairment of DNA repair. Whereas, deficiency worsen these and aids the aging process [22][23][24]. To generate adequate vitamin D *in situ,* one needs to have a healthy balance of sun exposure in favor of benefits while avoiding potential harmful effects [25][26][27].

3. Role of Calcitriol on Aging Process

Advancing age promotes cellular accumulation of toxic products, particularly those related to oxidative stress such as methylation of DNA. In conjunction with mitochondrial dysfunction and reduced viability of cells, lead to premature cell deaths [28]. It also reduces the immune functions, immune-senescence, together with inflammation, as demonstrable with increased circulating pro-inflammatory cytokines [29][30]. Combination of these contribute to many age-related disorders, such as Alzheimer's disease, cardiovascular and pulmonary diseases, and increased susceptibility to autoimmunity and infections [29][30].

4. Preventative Effects of Vitamin D on Inflammation and Oxidative Stress

Vitamin D works in conjunction with micronutrients, vitamins and antioxidants. In the presence of physiological serum 25(OH)D concentration of between 30 and 60 ng/mL (75 and 150 nmol/L), metabolomics, transcriptomics, epigenetics effects of vitamin D [31] and suppression of oxidative stress and systemic inflammation, lead to improved clinical outcomes.

The benefits derived from savings and reducing the risks of common diseases by increasing the population serum 25(OH)D concentrations beyond 30 ng/mL, are orders of magnitude higher that the vitamin D deficiency associated investigations and treatment costs. Thus, a country-wide replacement of vitamin D is a highly cost-effective public health approach that would lead to tangible positive impact on people and the economy.

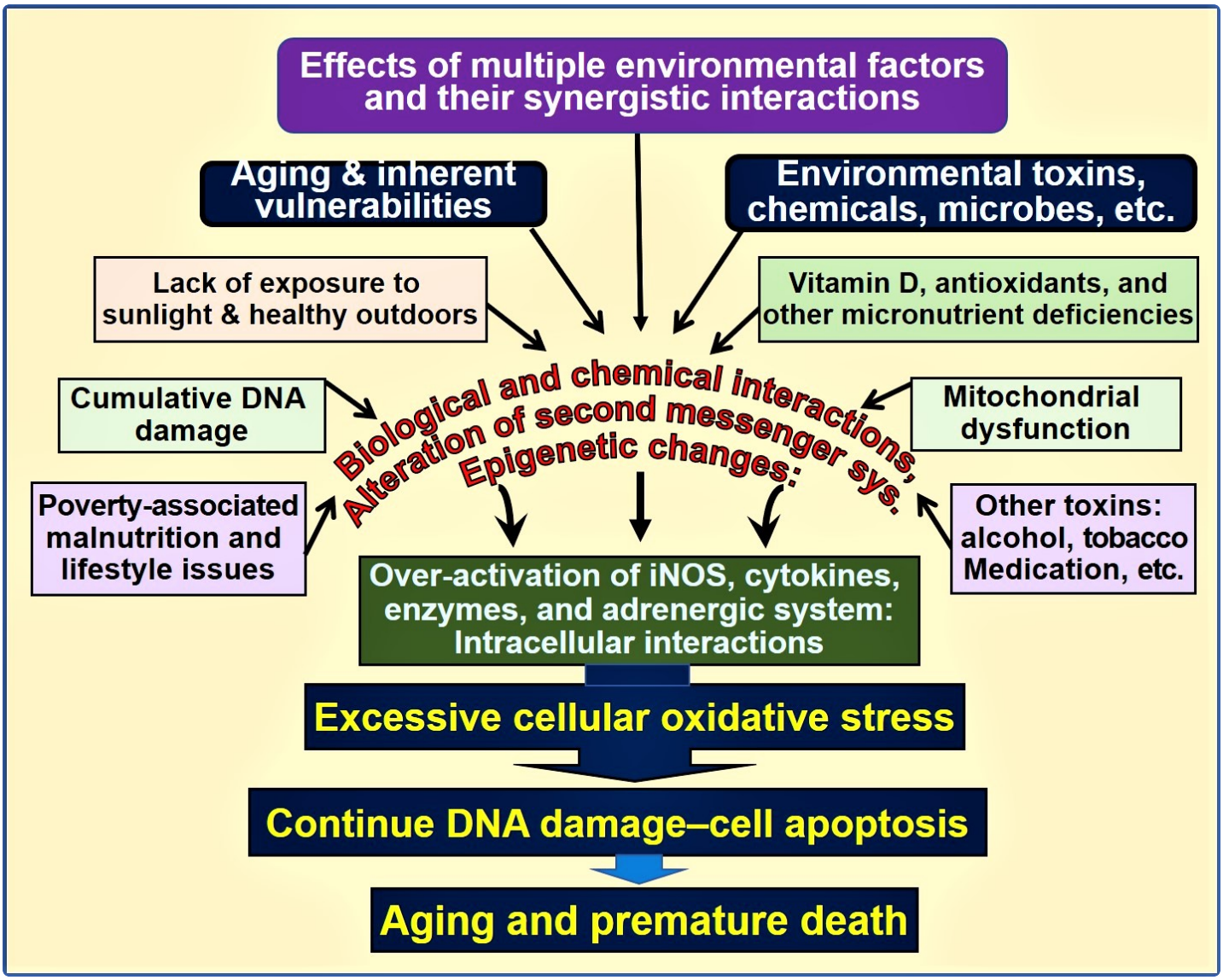

Figure 1. Environmental, microbial, biological and chemical interactions that modify DNA and mitochondrial functions and epigenetics, which modifies the aging process. Vitamin D deficiency is one of many factors that enhances this oxidative-stress cycle, accelerating premature cell death [abbreviations used: DNA = deoxyribonucleic acid; iNOS = inducible nitric oxide enzyme].

Normal serum concentrations of both 25(OH)D and 1,25$(OH)_2$D are essential for optimal cellular function and protect from the excessive oxidative stress-related DNA damage.

5. Conclusion

However, increased risk for illnesses and reduced longevity can occur despite the presence of physiologic concentrations of calcitriol because this is not the only mechanism protecting cells from oxidative stress. For reductions in the incidence of diseases, longer-term maintenance of a steady state of the serum 25(OH)D concentration is necessary [32]. The minimal level is considered to be 30 ng/mL (50 nmol/L), while the optimal range is between 30 and 60 ng/mL [33].

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