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Changes in vitamin D endocrinology during aging in adults

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ABSTRACT

Worldwide, vitamin D deficiency is a common finding. Within individuals 25-hydroxyvitamin D (25OH) D) concentrations remain fairly stable over time although large differences in individual longitudinal changes exist. During aging vitamin D metabolism and activity changes in several different ways. Intestinal resistance to 1,25(OH)2D develops which hampers intestinal calcium uptake. Vitamin D receptor number decreases with aging in several organs involved in calcium metabolism and 1alpha-hydroxylase activity decreases mainly due to a decrease in renal function reducing vitamin D activation. Effects of 1,25(OH)2D on cell proliferation and differentiation may influence potential anti-cancer effects whereas regulation of telomere length may result in longevity. In older individuals, vitamin D supplementation has positive effects on fracture risk, number of falls and physical function. Supplementation in older populations warrants specific attention. Effects on “non-classical” outcomes may be revealed by ongoing large randomized clinical trials with high doses of vitamin D.

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Abbreviations: 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)2D, 1,25dihydroxyvitamin D; 24,25(OH)2D, 24,25-dihydroxyvitamin D; CYP2R1, 25-hydroxylase; CYP27B1, 1alpha-hydroxylase; CYP24A1, 24-hydroxylase; VDR, vitamin D receptor; FGF-23, fibroblast growth factor 23.

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1. Introduction

Vitamin D is primarily produced in the skin under the influence of UV-B light of the sun on 7-dehydrocholesterol. In most adult individuals, dietary intake of vitamin D, from sources such as fatty fish, provides only a small additional contribution to vitamin D status. In older individuals, dietary intake becomes more important. Vitamin D requires two hydroxylation steps to become fully activated. The first step occurs in the liver by 25-hydroxylase (CYP2R1), which produces 25-hydroxyvitamin D (25(OH)D). The second step involves hydroxylation by 1 alpha-hydroxylase (CYP27B1) to 1,25-dihydroxyvitamin D (1,25(OH)2D) mainly in the kidney. 25(OH)D is the predominant circulating form of vitamin D mostly bound to vitamin D binding protein. 25(OH)D has a long half-life in contrast to 1,25(OH)2D and is generally considered the best marker of vitamin D status. When 1,25(OH)2D is sufficiently present, 24,25-dihydroxyvitamin D (24,25(OH)2D) is formed in the kidney by 24-hydroxylase (CYP24A1) and further catabolized. A number of extra-renal tissues are able to convert 25(OH)D to 1,25(OH)2D. The 1,25(OH)2D produced by these tissues appears to act locally in an autocrine or paracrine fashion and does not contribute significantly to the circulating 1,25(OH)2D concentrations (Lips, 2006).

Vitamin D exerts its effects on the one hand through genomic effects by binding to the nuclear vitamin D receptor (VDR) and vitamin D responsive elements of many genes and on the other hand through rapid non-genomic effects through a postulated membrane receptor and second messengers (Cesari et al., 2011). VDR is present throughout the body in many different cell types such as immune, muscle and bone cells. Vitamin D is essential for the efficient intestinal absorption of calcium and phosphate to create sufficient local concentrations of calcium and phosphate for adequate bone mineralization. Vitamin D in children has mainly been recognized for its important role in bone health. A deficiency of 25(OH)D in children may result in the clinical picture of rickets in which defective mineralization or calcification of bones before epiphyseal closure leads to fractures and deformities. Inadequate mineralization of bone at adult and older age results in osteomalacia and is often the result of deficient concentrations of 25(OH)D. Low concentrations of 25(OH)D also contribute to the development of osteopenia and osteoporosis through an increase in parathyroid hormone concentrations and an increase in bone turnover (Lips, 2006; van Schoor et al., 2008). Vitamin D deficiency also predicts functional decline and sarcopenia at older age (Sohl et al., 2013; Visser et al., 2003). Through these mechanisms 25(OH)D is a determinant of falls and fractures in older populations. Last decades, vitamin D deficiency has been associated with a wide spectrum of age-related diseases such as diabetes mellitus type 2, cardiovascular disease and cancer, in particular in older individuals (Meehan and Penckofer, 2014). Causality for these so-called “non-classical” outcomes, however, remains to be established. The clinical consequences of deficient 25(OH)D concentrations warrant a sufficient level at all ages. Special attention may be given to 25(OH)D concentrations in older individuals because they are characterized, amongst others, by a high prevalence of falls and fractures.

In the present review we aim to present an overview of different factors contributing to changes in vitamin D endocrinology during the aging process. Hereby we will focus on the human adult. We will go further into the potential role of vitamin D in cellular aging and telomere biology. Finally, we will discuss the potential consequences of these changes on human health and disease.

2. Prevalence and risk factors of vitamin D deficiency

The formation of active 1,25(OH)2D by 1-alpha hydroxylase is dependent on sufficient availability of the substrate 25(OH)D. The prevalence of 25(OH)D concentrations below 50 nmol/L is still a widespread problem worldwide (Cashman et al., 2016; Mithal et al., 2009; Looker et al., 2011; van Schoor and Lips, 2011). Vitamin D deficiency affects all age groups, from the newborn to the older adult, and is dependent on several lifestyle and environmental conditions. Specific risk groups for vitamin D deficiency are young children, pregnant women, older persons in particular institutionalized and home-bound individuals, and non-western immigrants. In Southeast Asia and Mongolia more than 90% of children and the young adult population has vitamin D deficiency. In the U.S. and Europe the percentage of older adults still living in the community having deficient 25(OH)D concentrations is also high and ranges from 20 to 100% (Cashman et al., 2016; Snijder et al., 2005). In institutionalized and home-bound individuals the prevalence of vitamin D deficiency is even higher (Earthman et al., 2012; Sohl et al., 2012). In general, older age, female sex, higher latitude, winter season, darker skin pigmentation, less sunlight exposure, low intake of vitamin D containing food, and absence of vitamin D fortification are the main factors that are associated with lower 25(OH)D concentrations worldwide (Cashman et al., 2016; Mithal et al., 2009; Looker et al., 2011; van Schoor and Lips, 2011).

Many factors potentially contribute to the presence of vitamin D deficiency at any age (Table 1). During the aging process, however, the contribution of these risk factors to the presence of low 25(OH)D concentrations changes (Gallagher, 2013). As the general population ages the relative amount of women compared to men increases. Most studies demonstrate that older women are more prone to be 25(OH)D deficient than older men (Mithal et al., 2009; van Schoor and Lips, 2011).

In the skin, previtamin D is produced by exposure of 7-dehydrocholesterol to ultraviolet (UV) radiation. Older individuals spent less time outdoors particularly if they are institutionalized or home-bound. In addition, the amount of 7-dehydrocholesterol in skin cells decreases as the body ages which in turn decreases the capacity to synthesize previtamin D (Zhou et al., 2006). Nevertheless, exposure to UV irradiation in older nursing-home residents is capable to increase 25(OH)D concentrations to the normal range with doses less than those required to produce erythema (van Schoor et al., 2014; Jorde et al., 2010).

In addition to sunlight-related factors, intake of vitamin D may change during aging. Dietary intake of vitamin D is generally low in all age groups and is unlikely to exceed 400 IU daily unless there is a lot of fish with high vitamin D content in the diet such as in some Scandinavian countries. Also, dietary intake is highly dependent on food fortification with vitamin D which occurs in the United States, Canada and some European countries including Finland and Sweden. In the United States an increase in total vitamin D intake was shown after the age of 50 years. This was caused by a higher amount of vitamin D supplementation use (Gallagher, 2013).

As adults age body composition changes towards more fat and less muscle mass. The amount of adipose tissue is inversely related to 25(OH)D concentrations (Snijder et al., 2005). Several mechanisms are hypothesized to contribute to this inverse relationship such as sequestration of vitamin D in adipose tissue, increased catabolism of vitamin D due to local CYP24A1in adipose tissue or diminished synthesis of 25(OH)D by the liver enzyme CYP2R1 (Earthman et al., 2012) in the presence of hepatic fat. Increased use of medications as often occurs during aging also influences 25(OH)D concentrations (Sohl et al., 2012; van Orten-Luiten et al., 2014). Some drugs such as anticonvulsants and rifampicin activate the nuclear steroid xenobiotic receptor which interacts with the VDR and probably regulates enzymes responsible for 1,25(OH)2D production and degradation (Zhou et al., 2006). Other drugs have also been shown to be related to lower 25(OH)D concentrations, for

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