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Review

Vitamin D metabolism and action in the prostate: Implications for health and disease

Srilatha Swami, Aruna V. Krishnan, David Feldman *

Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA

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ABSTRACT

Prostate cancer (PCa) is the second most common cancer in men worldwide. Epidemiological, molecular, and cellular studies have implicated vitamin D deficiency as a risk factor for the development and/or progression of PCa. Studies using cell culture systems and animal models suggest that vitamin D acts to reduce the growth of PCa through regulation of cellular proliferation and differentiation. However, although preclinical studies provide a strong indication for anti-cancer activity, proof of therapeutic benefits in men is still lacking. The anti-proliferative and pro-differentiating properties of vitamin D have been attributed to calcitriol [1,25$(OH)_2D_3$], the hormonally active form of vitamin D, acting through the vitamin D receptor (VDR). Metabolism of vitamin D in target tissues is mediated by two key enzymes: 1α-hydroxylase (CYP27B1), which catalyzes the synthesis of calcitriol from 25(OH)D and 24-hydroxylase (CYP24), which catalyzes the initial step in the conversion of calcitriol to less active metabolites. Many factors affect the balance of calcitriol synthesis and catabolism and several maneuvers, like combination therapy of calcitriol with other drugs, have been explored to treat PCa and reduce its risk. The current paper is an overview addressing some of the key factors that influence the biological actions of vitamin D and its metabolites in the treatment and/or prevention of PCa.

Contents

* Corresponding author. Address: Department of Medicine/Endocrinology, Stanford University School of Medicine, 300 Pasteur Drive, Room S-025, Stanford, CA 94305-5103, USA. Tel.: +1 650 725 2910; fax: +1 650 725 7085.
E-mail address: dfeldman@stanford.edu (D. Feldman).

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1. Introduction

Prostate cancer (PCa) is the most commonly diagnosed malignancy in American men, excluding skin cancer (Jemal et al., 2010). In men over the age of 50, sub-clinical PCa is found in as many as 40% of individuals (Stamey et al., 1993). Although PCa is generally a slowly progressing malignancy, mortality from this disease is nonetheless considerable. In contrast to many other malignancies, the incidence of PCa has continued to rise each year and currently PCa is the second leading cause of cancer in men. Its prevention and treatment has remained an ongoing challenge for clinicians worldwide.

This review will discuss the potential benefits of vitamin D and its active metabolites in preventing and treating PCa. The dietary forms of vitamin D include ergocalciferol (vitamin D_2) from plants, and vitamin D_3 from animal products, which is the human form of the hormone. Vitamin D_3 is approximately 87% more potent in raising and maintaining serum 25-hydroxyvitamin D [25(OH)D] concentrations and produces 2- to 3-fold greater storage of vitamin D than does equimolar vitamin D_2 (Heaney et al., 2011). This review will subsequently focus exclusively on vitamin D_3 and refer to it simply as vitamin D.

Vitamin D, a fat-soluble pro-hormone is synthesized in the body in response to sunlight and is converted to the active hormone 1,25-dihydroxyvitmin D_3 (calcitriol). Considerable preclinical and epidemiologic data suggest that vitamin D deficiency may play a role in the pathogenesis and progression of PCa, and that vitamin D or its active form, calcitriol, may be useful in the prevention or treatment of the disease. The anti-cancer properties of vitamin D have been attributed primarily to calcitriol, the hormonally active form of vitamin D. Measurement of vitamin D levels in many studies, including both surrogate estimates of vitamin D (e.g. sunlight exposure and diet) as well as assay of serum 25(OH)D, the circulating precursor for calcitriol, indicate that vitamin D deficiency increases the risk of PCa, although not all studies agree.

Several recent reviews discuss the role of vitamin D in PCa (Beer and Myrthue, 2006; Deeb et al., 2007; Fleet, 2008; Gombart et al., 2006; Kahraman et al., 2004; Krishnan and Feldman, 2010a,b; Krishnan et al., 2010; Stewart and Weigel, 2004). Based upon epidemiological studies, several risk factors such as age and genetics have been identified for PCa (Kozlowski and Grayhack, 1995; Ruijter et al., 1999). Studies published by Garland and Garland (1980) and Schwartz and colleagues (Hanchette and Schwartz, 1992; Schwartz and Hulka, 1990) suggest a role for sunlight (a surrogate for vitamin D) in decreasing the risk of developing different cancers in humans. It has been shown that African American individuals have lower serum 25(OH)D levels as a result of their darker skin pigmentation. Melanin in the darkly pigmented skin of an African American individual absorbs UV radiation, inhibiting the formation of vitamin D_3 in the basal layer of the epidermis (Bell et al., 1985). This offers a plausible but unproven explanation for the higher incidence of PCa in African Americans when compared to their Caucasian counterparts (Studzinski and Moore, 1995). Many epidemiologic studies have examined whether vitamin D deficiency increases the risk of PCa. Although some demonstrate increased risk of PCa associated with deficiency, the various studies have not shown consistent results and some fail to show an inverse correlation. A recent review by Giovannucci discusses vitamin D deficiency in several cancers (Giovannucci, 2009).

Many preclinical studies indicate that exposing cancer cells to high concentrations of calcitriol arrests progression through the cell cycle, induces apoptosis and slows or stops tumor growth *in vivo* (Blutt et al., 2000; Yang and Burnstein, 2003). Calcitriol also potentiates the anti-tumor activity of a number of types of cytotoxic anti-cancer agents in preclinical models (Hershberger et al., 2001). Thus, studies of vitamin D and PCa have advanced from the hypothesis that vitamin D deficiency increases the risk of PCa to intervention trials of vitamin D in PCa patients. This review is aimed at addressing some of the key factors that influence the biological actions of vitamin D and its metabolites in the treatment and/or prevention of PCa.

2. Vitamin D actions

Although the role of calcitriol in maintaining calcium homeostasis has been known for a long time, it is only recently that investigators have begun to understand the broader scope of calcitriol actions (Feldman et al., 2001). In studying the role of calcitriol in cancer it is imperative to study the various factors that influence the cell- or tissue-specific actions of calcitriol. These include vitamin D receptor (VDR) expression and ligand interactions, as well as local synthesis, metabolism and transport of vitamin D and its metabolites.

2.1. Vitamin D receptor and prostate cancer

Although the initial description of the vitamin D receptor (VDR) in the prostate and most of the subsequent investigation of calcitriol actions have centered around PCa cell lines, calcitriol also appears to play an important role in normal prostate tissue. Peehl et al. (1994) reported the presence of VDR in freshly obtained surgical prostate specimens as well as primary cultures of epithelial and stromal cells of the prostate (Peehl, 2004). Primary cultures from surgical specimens of benign prostatic hyperplasia (BPH) also express VDR (Peehl et al., 1994). Although VDR is present in both epithelial and stromal cells cultured separately, lower levels of VDR were seen in the stromal fibroblasts compared to cells of the glandular epithelium. The region of origin within the prostate tissue did not influence the abundance of VDR, as both the peripheral zone and central zone cultures had similar VDR content (Peehl et al., 1994). Krill et al. (2001) studied VDR expression in normal prostate glands from donors of various age groups and found that VDR expression changed with age with peak levels in the fifth decade and a decline thereafter. Calcitriol exerts anti-proliferative effects on rat neonatal prostatic epithelial cells (Konety et al., 2000) and human prostatic epithelial cells (Krill et al., 1999). Konety et al. (1999, 2000) showed that exposure of rat pups *in utero* to ip injections of calcitriol (1.25 μg every other day) influenced prostatic growth and differentiation throughout the lives of the animals. In general, all these studies support a role for vitamin D in normal prostate physiology and growth.

The finding by Miller et al. (1992) of the presence of VDR in LNCaP human PCa cells was an important early finding. The demonstration of VDR and the anti-proliferative actions of calcitriol (1–100 nM) in three different PCa cell lines including LNCaP, PC-3 and DU 145 cells by Skowronski et al. (1993) initiated the subsequent research into the investigation of the direct role that vitamin D plays in prostate biology and how the hormone might be beneficial for therapy of PCa.

2.2. Vitamin D metabolism in prostate

Metabolism of vitamin D in target tissues is mediated by two key enzymes: 1α-hydroxylase (CYP27B1), which catalyzes the synthesis of calcitriol from 25(OH)D and 24-hydroxylase (CYP24), which catalyzes the initial step in the conversion of calcitriol to less active metabolites. Thus, the ratios of these two enzymes play an important role in determining the intracellular concentration of vitamin D metabolites and their biological activities.