



Tower Cancer Research Foundation

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Vitamin D and Cancer

Biologically active vitamin D (calcitriol) actually is a steroid hormone. It is well known to play a crucial role in regulating body levels of calcium and phosphorus, and bone mineralization. Recently it has become evident that receptors for vitamin D are present in almost all cells, raising the possibility that this hormone has widespread biological effects that may include regulation of cell differentiation and proliferation ².

Synthesis and Physiology

Vitamin D₃ is produced in the skin after light energy (UVB) is absorbed by a precursor molecule. In addition, there are dietary sources of D₃ such as fortified milk and cereals, egg yolk, fatty fish (especially wild salmon); certain plants contain vitamin D₂. Typically, the usual diet does not contain enough vitamin D to prevent deficiencies, and exposure to sunlight is more important. Vitamins D₃ and D₂ do not have significant biological activity and must be metabolized first by liver 25-hydroxylase to 25-hydroxycholecalciferol, and then by kidney 1-alpha-hydroxylase to the physiologically active form, 1,25-dihydroxycholecalciferol. The half-life of 25-hydroxycholecalciferol is several weeks, while that of the active hormone, 1,25 hydroxycholecalciferol, is just a few hours ².

The major inducer of the key enzyme 1-alpha-hydroxylase is parathyroid hormone (PTH), but hypophosphatemia has a role as well ². Once activated, the most important functions of vitamin D are to enhance intestinal absorption and renal resorption of calcium and regulate the balance of calcium and phosphorus to support bone mineralization ^{1,2}.

Potential for Widespread Biological Effects

Recent research has discovered that 1-alpha hydroxylase is expressed not only in the kidneys but also in many tissues, and also that receptors for active vitamin D are present in most cells ². Thus many, if not most, tissues have the capacity to convert inactive to active D, which is thought to bind to nuclear receptors involved in the regulation of genes responsible for controlling cell proliferation, differentiation, apoptosis, and adhesion. Vitamin D receptors therefore function as nuclear transcription factors and are involved in cell growth ^{2,3}.

These discoveries have led to the hypothesis that vitamin D may be a major regulator of cell function, and also the corollary that low levels may lead to abnormal transcription increasing the potential for mutations. This theory is supported by experimental observations using cultured cells that demonstrate potent effects of D on cell growth and differentiation ^{2,3}.

Epidemiology of Vitamin D Deficiency

Because the half-life of 1,25 di(OH)D is so rapid, serum measurements of vitamin D are performed on its precursor 25(OH) D. To determine the prevalence of vitamin D deficiency in the male and female US population of varying ages, vitamin D levels of about 19,000 individuals drawn between 1988 and 1994 were compared to 13,000 individuals drawn between 2001 and 2004. Results showed that the mean value was normal during the earlier time period, but dropped into the insufficient range (24 ng/ml) in the latter period, with more than one third of those tested overtly deficient (<20 ng/ml). The prevalence of D deficiency was about the same for men and women, and age was not a factor, but dark-skinned and overtly obese individuals were more likely to be deficient ⁴. This study indicated that vitamin D deficiency has become exceedingly common in the American population, and this trend is worsening. The main causes in adults are inadequate sun exposure (widespread use of sunscreen), deficient diet, and pregnancy/ lactation ¹. Deficiency is more prevalent in obese individuals because vitamin D is fat soluble impairing

the maintenance of normal blood levels. Also, individuals with dark skin pigmentation do not synthesize D optimally because melanin absorbs the UVB rays of the sun. Certain medical diseases, especially those with malabsorption, may be factors as well ¹.

Is There a Relationship To Cancer?

In a recent study of 512 consecutive women (mean age 50) with newly diagnosed breast cancer, surprisingly, 76% were found to be vitamin D deficient at presentation; only 24% had normal levels. With a mean follow-up of 11.6 years, the patients presenting initially with low D levels were almost twice as likely to develop metastatic disease and also had significantly reduced overall cancer-related survival ⁵. The association between vitamin D deficiency and a poor outcome was striking.

Evidence that there may be an actual cause and effect relationship between vitamin D and cancer has been presumed from other studies. The most persuasive was an ecological study that found higher breast cancer rates in northern latitudes where there is less sun exposure ⁶. Other observational studies dealing with cancer risk in general have yielded very inconsistent results ⁷. Possibly the largest prospective study involving 16,818 participants followed for 146,578 patient-years found no relation between total cancer mortality and vitamin D status⁸. However, the study reported an interesting exception to this conclusion because it found an inverse relationship between vitamin D levels and colorectal mortality, with normal levels or higher associated with a 72% risk reduction⁸. Furthermore, this was not an isolated observation, as other reports, including the large Nurses' Health Study, have reported reduced colorectal cancer and adenoma risk associated with normal or higher levels of vitamin D. The Women's Health Initiative involving 32,000 postmenopausal women attempted to test this possible relationship by studying whether cancer could be prevented by supplementing vitamin D at 400 IU/day ⁷. The results indicated no statistical effect on the incidence of colorectal cancer, but the study was criticized because only low doses of D were administered ⁷. Also, there are recent reports that vitamin D does not prevent prostate ¹⁰ or pancreas ⁹ cancer, despite earlier reports to the contrary. In fact, higher than normal blood levels of vitamin D have been associated with increased risk for prostate and esophageal cancer ⁷.

Although it is clear that vitamin D has potential for major biological effects, the cumulative data currently is conflicting and inadequate to conclude whether it has any influence on cancer prevention or mortality ⁷.

However, it is clearly established that cancer patients are especially prone to vitamin D deficiency. About 75% of breast cancer survivors had insufficient levels in one study, and colorectal patients on chemotherapy as compared to those off treatment, also had very low levels ¹¹. Although all women need adequate D for bone health, cancer patients in particular, both men and women, need monitoring and supplementation. In addition, certain cancer treatments, such as aromatase inhibitors in women with breast cancer, and androgen deprivation therapy for men with prostate cancer, promote osteopenia and osteoporosis. The goal for monitoring cancer as well as normal patients is 25(OH) D levels of 30-40 ng/mL (or 75-100 nmol/L). Toxic levels exceed 150 ng/mL.

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