

Sunlight, season, skin pigmentation, vitamin D, and 25-hydroxyvitamin D: integral components of the vitamin D endocrine system^{1,2}

Anthony W Norman

It is likely that some but not all readers of the article by Harris and Dawson-Hughes (1) in this issue of the Journal may be surprised to find a paper discussing the relations between winter and summer on the plasma concentration of 25-hydroxyvitamin D₃ (calcidiol) as being an important nutritional health issue relevant to black and white women. It is hoped that newcomers to the field will use this article as an opportunity to gain some insight into one of the many chapters that constitute our modern understanding of the vitamin D endocrine system (2), whereas vitamin D aficionados will be interested to learn the latest details in this intriguing chapter.

A fundamental fact that must be accepted to fully understand the article by Harris and Dawson-Hughes is that vitamin D is not really a vitamin, ie, it is not an essential dietary factor, but is a prohormone that is produced photochemically in the skin from 7-dehydrocholesterol. It is largely through a historical accident that vitamin D was classified in the early 1920s as a vitamin rather than as a steroid hormone (15). The molecular structure of vitamin D is closely allied to that of classic steroid hormones (eg, estradiol, cortisol, and aldosterone) because they all have the same root cyclopentanoperhydrophenanthrene ring structure. Technically, vitamin D is a secosteroid. Secosteroids are those steroids in which one of the rings of the cyclopentanoperhydrophenanthrene structure has undergone breakage of a carbon-carbon bond; for vitamin D, this is the 9,10 carbon-carbon bond of ring B (Figure 1). Given this fact as a starting point, it is important to understand some of the details of the sunlight-mediated photochemical conversion of 7-dehydrocholesterol into vitamin D₃ (cholecalciferol) (Figure 1).

After production of vitamin D₃ in the skin, the plasma transport protein vitamin D-binding protein (DBP) is responsible for picking up the vitamin D₃ and delivering it, along with the many vitamin D metabolites that it also binds, to all the elements of the vitamin D endocrine system (2). The first stop for vitamin D₃ is normally the liver, where it is metabolized into 25-hydroxyvitamin D₃. The metabolite 25-hydroxyvitamin D₃ is the major circulating metabolite of vitamin D₃ and an understanding of its plasma concentration has come to be accepted as being clinically a more important marker of vitamin D nutritional state than is knowledge of the plasma vitamin D concentration (5-7). 25-Hydroxyvitamin D₃ is transported by DBP to the kidney, which is the endocrine gland that produces the two steroid hormones 1 α ,25-dihydroxyvitamin D₃ (calcitriol) and the candidate hormone 24R,25-dihydroxyvitamin D₃. DBP then transports both secosteroids to their target tissues where appropriate bio-

logical responses are mediated. 1 α ,25-dihydroxyvitamin D₃ is considered to be the hormonally active form of vitamin D₃; >30 tissues are known to have nuclear receptors for this secosteroid (2). Recent evidence supports the view that 24R,25-dihydroxyvitamin D₃ is also an important steroid hormone with receptors in fracture-healing bone tissue and cartilage (8).

The next lesson for the interested reader is an introduction to the cellular anatomy of skin. Skin consists of two primary layers: the inner dermis, composed largely of connective tissue, and the outer thinner epidermis. The thickness of the outer epidermis is \approx 25 μ m, or about the thickness of one page of this journal, whereas the thickness of the dermis is 1-2 mm. The epidermis contains five strata; from outer to inner they are respectively as follows: strata corneum, lucidum, granulosum, spinosum, and basale. For the purposes of the article under discussion, the reader needs to know that the highest concentrations of 7-dehydrocholesterol are found in the stratum basale and stratum spinosum. Accordingly, these two layers have the greatest capability for production of previtamin D₃ and vitamin D₃, whereas the other layers have a lesser capability.

Several types of cells characterize the epidermis. The most prevalent cells are the keratinocytes, which synthesize and excrete the insoluble keratin that strengthens and waterproofs the outer surface of the skin. The second most prevalent cells are the melanocyte cells, which produce the pigment melanin. The skin color characteristic of racial groups is determined primarily by the epidermal melanin content (9). The melanocytes are mostly located in the innermost layer of the epidermis, the stratum basale. Here the enzyme tyrosinase synthesizes melanin from tyrosine. Importantly, the pigment granules, which contain the melanin, are transferred from the tips of long cytoplasmic processes of the melanocyte cells to other adjacent epidermal cells, which are migrating upward toward the outer surface. Thus, melanin is present in all five of the epidermal strata and is the responsible agent that imparts a characteristic coloration to the skin. It normally takes 2 wk for a cell in the stratum basale to migrate up to the stratum corneum and another 2 wk for the cell remnants to slough off.

The final lesson is a consideration of the four important variables that collectively determine the amount of vitamin D₃ that

¹ From the Department of Biochemistry & Division of Biomedical Sciences, University of California-Riverside.

² Reprints not available. Address correspondence requests to AW Norman, Department of Biochemistry, University of California-Riverside, Riverside, CA 92521. E-mail: norman@ucr.ac1.ucr.edu.

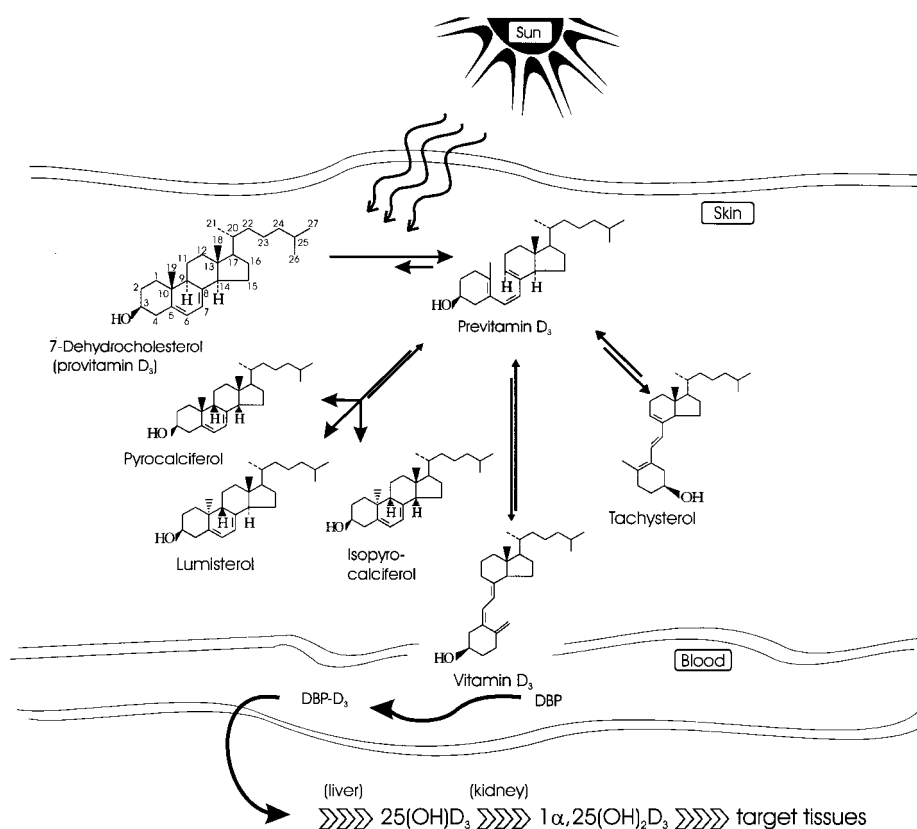


FIGURE 1. Photochemical pathway occurring in the skin that describes the production of vitamin D₃ (cholecalciferol) from 7-dehydrocholesterol. A brief description of the cellular anatomy of skin is provided in the text. The starting point is the irradiation of a provitamin D, which contains the mandatory $\Delta^{5,7}$ -conjugated double bonds; in the skin the highest concentrations of 7-dehydrocholesterol are present in the stratum spinosum and stratum basale. After absorption of a quantum of light from sunlight [ultraviolet (UV)-B], the activated molecule can return to its ground state and generate at least six distinct products. The four steroids that do not have a broken 9,10 carbon bond (the starting 7-dehydrocholesterol and the products pyrocalciferol, lumisterol, and isopyrocalciferol) represent four diastereoisomers with either an α - or β -orientation of the methyl group on C-10 and the hydrogen on C-9. The three secosteroid products all have a broken 9,10 carbon-carbon bond with a differing position of the three conjugated double bonds; they include previtamin D₃, vitamin D₃, and tachysterol. In the skin the principal irradiation product produced is previtamin D₃, which then undergoes a 1,7-sigmatropic hydrogen transfer from C-19 to C-9, yielding the final vitamin D₃. Under normal sunlight exposure, irrespective of the extent of skin pigmentation, the amount of previtamin D₃ produced is not greater than $\approx 15\%$ of the available substrate 7-dehydrocholesterol (11). Further UV exposure simply causes the photoisomerization of previtamin D₃ to lumisterol and tachysterol, which are both biologically inert. The newly produced vitamin D₃ that is formed in the skin is removed by binding to the plasma transport protein, the vitamin D-binding protein (DBP), present in the capillary bed of the dermis. DBP-vitamin D₃ then enters the general circulatory system where it ultimately can be metabolized in the liver to 25-hydroxyvitamin D₃ [25(OH)D₃, or calcidiol] and then in the kidney to 1 α ,25-dihydroxyvitamin D₃ [1 α ,25(OH)₂D₃, or calcitriol].

will be photochemically produced by an exposure of skin to sunlight. The two principal determinants are the quantity (intensity) and quality (appropriate wavelength) of the ultraviolet (UV) B irradiation reaching the 7-dehydrocholesterol deep in the stratum basale and stratum spinosum. 7-Dehydrocholesterol absorbs UV light most efficiently over the wavelengths of 270–290 nm and thus only UV light in this wavelength range has the capability to produce vitamin D₃. There have been many studies showing the influence of season and latitude on the cutaneous photochemical synthesis of vitamin D₃ (10, 11); maximal vitamin D₃ production occurs in summer months and, depending on latitude, little or no vitamin D₃ may be generated in winter months.

A third factor, of course, is the actual concentration of 7-dehydrocholesterol in these two strata. Under normal physiologic circumstances in humans there are ample quantities of 7-dehydrocholesterol available in the stratum spinosum and

stratum basale (≈ 25 – $50 \mu\text{g}/\text{cm}^2$ of skin) but in some species, such as domestic cats, this is an important consideration. Morris (12) reported that kittens exposed to UV-B are unable to photochemically produce vitamin D₃. The concentration of 7-dehydrocholesterol in cat skin, in contrast with skin in hamsters, rats, pigs, and sheep, was virtually undetectable. Thus, it may be that for domestic cats vitamin D₃ is an essential dietary trace nutrient, ie, a vitamin.

The fourth determinant of vitamin D₃ production is the concentration of melanin in the skin. Melanin, which absorbs UV-B in the 290–320 nm range, functions as a light filter and therefore determines the proportion of the incident UV-B that is actually able to penetrate the outer three strata and arrive at the stratum basale and stratum spinosum (13). Appreciation of this fact allowed Loomis (14) to propose that the evolution of the world's racial distribution by latitude was due to regulation of vitamin D


production. As people migrated to higher latitudes, their skin pigmentation was diminished to enable the adequate production of the vitamin by the skin.

Thus, skin pigmentation is, in fact, a dominant variable regulating the production of vitamin D₃ under circumstances of low levels of irradiation because melanin absorbs UV photons in competition with 7-dehydrocholesterol (4, 15). Armed with this background information, the reader should now understand the relations operative between skin pigmentation (blacks compared with whites), seasons (with seasonally varying UV-B intensities), and the conversion of 7-dehydrocholesterol into vitamin D₃ and then its subsequent metabolism by the vitamin D endocrine system to produce 25-hydroxyvitamin D₃ and ultimately 1 α , 25-dihydroxyvitamin D₃.

The principal message of the article by Harris and Dawson-Hughes is that circulating concentrations of 25-hydroxyvitamin D₃ were substantially and significantly lower in black than in white women in both the winter (February-March) and summer (June-July) months. Although there have been several publications describing lower concentrations of 25-hydroxyvitamin D₃ in dark-skinned people (13, 16-18), there is no question that the data from the study by Harris and Dawson-Hughes are the most convincing. Harris and Dawson-Hughes's study was large and well controlled; it included 51 black and 39 white women from Boston who were matched with respect to age and dietary intake of calcium and vitamin D (206 IU/d) (1).

As clearly documented in their Figure 1, the plasma 25-hydroxyvitamin D₃ concentrations of the black women were <50% of those of the white women in all four seasons of the year. Also apparent in both groups was the characteristic seasonal variation in plasma 25-hydroxyvitamin D₃ concentrations. In absolute terms, 25-hydroxyvitamin D₃ concentrations in the black and white women were 30.2 \pm 19.7 and 60.0 \pm 21.4 nmol/L (February-March) and 41.6 \pm 16.4 and 85.4 \pm 33.0 nmol/L (June-July), respectively, which suggests that the black women might be considered to have a marginal state of vitamin D nutrition. This then might be expected to have implications for nutritional recommendations and guidelines of what are appropriate vitamin D intakes for racial groups with extensive skin pigmentation. However, this is apparently not necessary because Matsuoka et al (13) clearly showed that there were differences in both vitamin D₃ and 25-hydroxyvitamin D₃ concentrations between blacks and whites, Harris and Dawson-Hughes showed that there were differences in 25-hydroxyvitamin D₃ concentrations between blacks and whites (their Table 1), and neither study showed significant differences in circulating concentrations of 1 α ,25-dihydroxyvitamin D₃ between blacks and whites.

Thus, as long as there are no unique biological responses of 25-hydroxyvitamin D₃ that cannot be supported by normal 1 α ,25-dihydroxyvitamin D₃ concentrations, then there may not be significant adverse health consequences attributable to the lower concentrations of 25-hydroxyvitamin D₃ when they are not below the range of 20-30 nmol/L. However, in Figure 2 of the article by Harris and Dawson-Hughes, where an inverse relation is shown between plasma 25-hydroxyvitamin D₃ concentrations in winter months and serum intact parathyroid hormone concentrations, a cautionary signal may be present. When 25-hydroxyvitamin D₃ concentrations fell below 30 nmol/L in black women, there was a distinct increase in intact parathyroid hormone concentrations to above-normal concentrations. In summary, the study by Harris and

Dawson-Hughes is a fine addition to the clinical nutritional literature concerning the vitamin D endocrine system and seasonal changes in 25-hydroxyvitamin D₃ concentrations in relation to skin pigmentation. 

REFERENCES

- Harris SS, Dawson-Hughes B. Seasonal changes in plasma 25-hydroxyvitamin D concentrations of young American black and white women. *Am J Clin Nutr* 1998;67:1232-6.
- Bouillon R, Okamura WH, Norman AW. Structure-function relationships in the vitamin D endocrine system. *Endocr Rev* 1995;16:200-57.
- Norman AW. Vitamin D: the calcium homeostatic steroid hormone. 1st ed. New York: Academic Press, 1979.
- Holick MF, MacLaughlin JA, Doppelt SH. Regulation of cutaneous previtamin D₃ photosynthesis in man: skin pigment is not an essential regulator. *Science* 1981;211:590-3.
- Mason RS. The clinical significance of vitamin D measurements. *Med J Aust* 1980;1/2:51 (letter).
- Velentzas C, Oreopoulos DG, Brandes L, Wilson DR, Marquez-Julio A. Abnormal vitamin-D levels. *Ann Intern Med* 1977;86:198 (letter).
- Garland CF, Comstock GW, Garland FC, Helsing KJ, Shaw EK, Gorham ED. Serum 25-hydroxyvitamin D and colon cancer: eight year prospective study. *Lancet* 1989;2:1176-8.
- Kato A, Seo E-G, Einhorn TA, Bishop JE, Norman AW. Studies on 24R,25-dihydroxyvitamin D₃: evidence for a non-nuclear membrane receptor in the chick tibial fracture-healing callus. *Bone* (in press).
- Byard PJ. Quantitative genetics of human skin color. *Yearbook Phys Anthropol* 1981;24:123-7.
- Stamp TCB, Round JM. Seasonal changes in human plasma levels of 25-hydroxyvitamin D. *Nature* 1974;247:563-5.
- Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D₃: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D₃ synthesis in human skin. *J Clin Endocrinol Metab* 1988;67:373-8.
- Morris JG. Ineffective vitamin D synthesis of vitamin D in kittens exposed to sun and ultraviolet light is reversed by an inhibitor of 7-dehydrocholesterol- Δ^7 -reductase. In: Norman AW, Bouillon R, Thomasset M, eds. Vitamin D: chemistry, biology and clinical applications of the steroid hormone. Riverside, CA: University of California, 1997:721-2.
- Matsuoka LY, Wortsman J, Haddad JG, Kolm P, Hollis BW. Racial pigmentation and the cutaneous synthesis of vitamin D. *Arch Dermatol* 1991;127:536-8.
- Loomis WF. Skin-pigment regulation of vitamin-D biosynthesis in man. Variation in solar ultraviolet at different latitudes may have caused racial differentiation in man. *Science* 1967;157:501-6.
- Holick MF, MacLaughlin JA, Clark MB, et al. Photosynthesis of previtamin D₃ in human skin and the physiologic consequences. *Science* 1980;210:203-5.
- Clemens TL, Adams JS, Henderson SL, Holick MF. Increased skin pigment reduces the capacity of skin to synthesize vitamin D₃. *Lancet* 1982;1:74-6.
- M'Buyamba-Kabangu JR, Fagard R, Lijnen P, Bouillon R, Lissens W, Amery A. Calcium, vitamin D-endocrine system, and parathyroid hormone in black and white males. *Calcif Tissue Int* 1987;41:70-4.
- Matsuoka LY, Wortsman J, Chen TC, Holick MF. Compensation for the interracial variance in the cutaneous synthesis of vitamin D. *J Lab Clin Med* 1995;126:452-7.

