THE RELATION BETWEEN SKIN DISORDERS AND VITAMIN D

Essay

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Introduction and Aim of the Work

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Vitamin D is a prohormone produced in the skin through ultraviolet irradiation of 7-dehydrocholesterol. It is biologically inert and must be metabolized to 25-hydroxyvitamin D in the liver and then to 1alpha,25-dihydroxyvitamin D in the kidney before function. The hormonal form of vitamin D, ie; 1alpha,25-dihydroxyvitamin D, acts through a nuclear receptor to carry out its many functions, including calcium and phosphate absorption in the intestine, calcium mobilization in the bone, and calcium reabsorption in the kidney. In addition, vitamin D has several non-calcemic functions in the body ***(Deluca, 2004).***

This overview provides a brief description of the physiologic, endocrinologic, and molecular biologic characteristics of vitamin D. It also provides information about new selective therapeutic analogues of vitamin D and highlights the role of vitamin D in pathogenesis and treatment of some inflammatory, infectious, autoimmune, neoplastic and other skin disorders.

Review of Literature

Chapter (1) Vitamin D

Chapter (1)

1. Vitamin D

1.1. Introduction

Vitamin D is a secosteroid (i.e., A steroid in which one of the bonds in the steroid rings is broken), fat-soluble prohormone of critical importance for a broad variety of independent physiological functions ***(DeLuca, 2004; Wolpowitz and Gilchrest, 2006; Holick, 2007).***It was identified after the discovery of the anti-rachitic effect of cod liver oil ***(Wolpowitz and Gilchrest, 2006).*** It is considered as a key regulator of bone metabolism and calcium and phosphorous homeostasis through a negative feedback with the parathyroid hormone *(PTH)* ***(DeLuca, 2004; Wolpowitz and Gilchrest, 2006; Holick, 2007).*** It also regulates the growth and differentiation of multiple cell types, and displays a number of immunoregulatory and anti-inflammatory properties ***(Adorini and Penna, 2008).***

It acts via binding to a corresponding intranuclear receptor [vitamin D receptor (VDR)], in target tissues ***(Stumpf et al., 1979; Gniadecki, 1996).*** Nearly, every tissue in the body has receptors for the active form of vitamin D ***(Di Rosa et al., 2011),*** including cells involved in innate and adaptive immune responses which can both produce and respond to the active form of vitamin D **(*Adorini and Penna*, 2008).**

1.2.Nomenclature of vitamin D precursors and metabolites

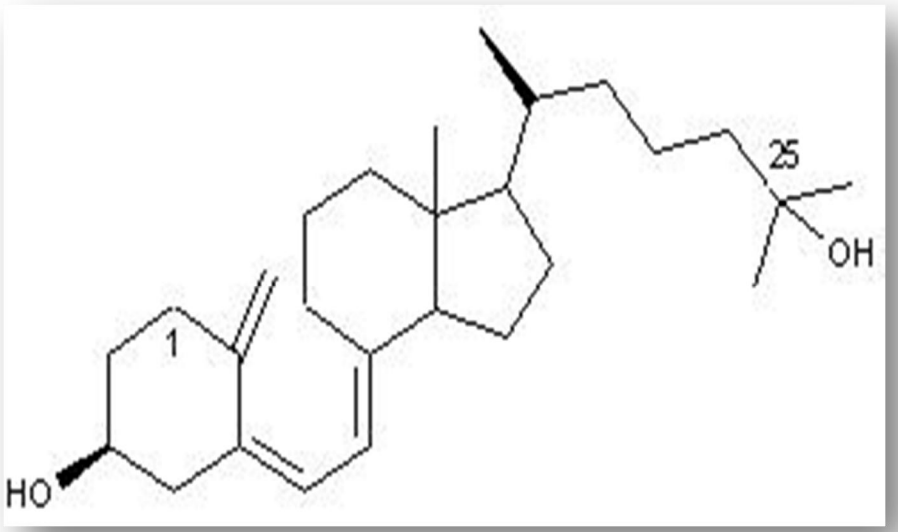
Vitamin D exits in nature in different forms as shown in table (1).

Table (1): Different forms, nomenclature and sources of vitamin D ***(Wolpowitz and Gilchrest, 2006).***

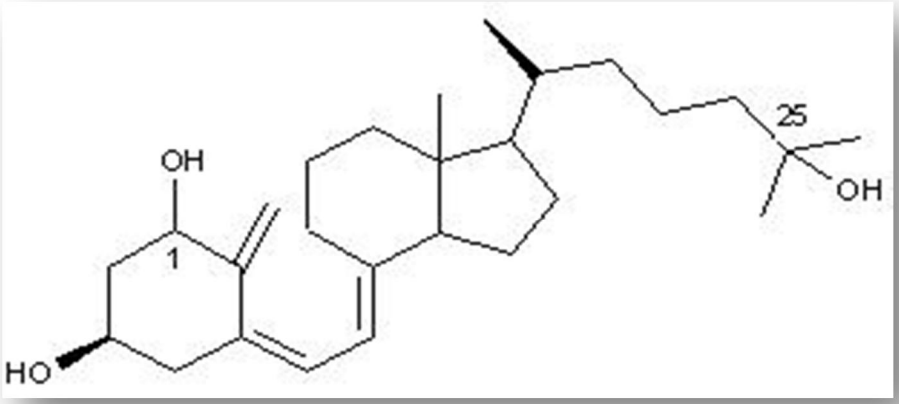
Common name	Clinical name	Abbreviation	Comments
7-Dehydrocholesterol	Provitamin D3	7-DHC	Lipid in cell membranes
Cholecalciferol	Previtamin D3	Previt D3	Photosynthesized in skin or obtained from diet
Ergocalciferol	Previtamin D2	Previt D2	Obtained from diet; equivalent to vit D3 as precursor for active vit D
Calcidiol	25-Hydroxyvitamin D	25-(OH) vit D	Circulating “storage” form ofY vit D, biologically inactive
Calcitriol	1,25-Dihydroxyvitamin D	1,25-(OH)2 vit D	Active form of vit D, tightly regulated

The two main forms of vitamin D in blood are ***25(OH)D (Calcidiol) (fig.1)***, the principal circulating form of vitamin D and ***1,25(OH) $_2$D(calcitriol) (fig. 2)*** , the principal active hormonal form of vitamin D and which is responsible for most of its biologic actions ***(Bikle,2009)***.

The difference in the chemical structure of the active metabolites is situated in the side chain ***(fig.1,2) (Feldman et al., 2005; Hollis and Wagner, 2004).*** 1,25$(OH)_2$D, is different from 25(OH) D in that it possesses an additional 1-alpha hydroxylation. This structural difference alters binding to the carrier protein [vitamin D binding protein (DBP)] as well as metabolism (***Bikle, 2009).***



(Fig.1): The Chemical Structure of Calcidiol *(Deluca, 2004).*

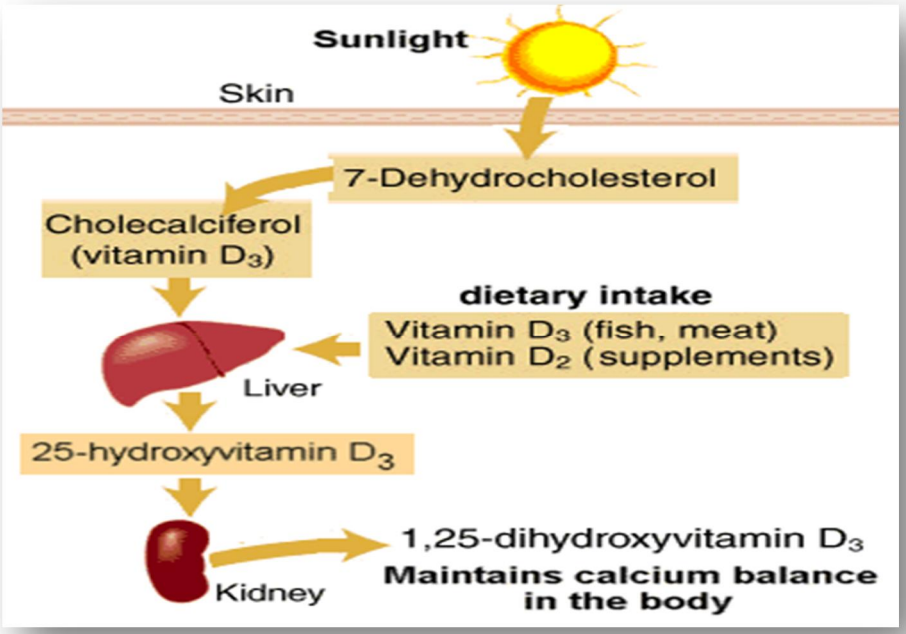


(Fig.2): The Chemical Structure of Calcitriol *(Deluca, 2004).*

1.3. Sources of Vitamin D

Vitamin D (1, 25$(OH)_2$D) is produced in relatively large quantities in humans and in the majority of vertebrate animals. The main production of 1, 25$(OH)_2$D occurs in the course of photosynthesis (Photochemical conversion of 7-dehydrocholesterol (7-DHC)to previtamin D in the skin), in the presence of ultraviolet (UV) light ***(Di Roso et al., 2011)*** during summer months ***(Feldman et al., 2005; Hollis and Wagner, 2004).*** Only a few foods naturally contain appreciable amounts of vitamin D: fish liver, fish liver oils, fatty fish, and egg yolks. Oily fish such as salmon, mackerel, and bluefish are excellent sources of vitamin D ***(Lu et al., 2007; Hollis and Wagner, 2004) (fig.3).*** Some countries practice fortification of certain foods with vitamin D, most often milk, margarine, and/or butter. The mean intake of

vitamin D, in different studies varies with age group, food, supplementation habits and gender ***(Lu et al., 2007; Hollis and Wagner, 2004).***



(Fig.3): Vitamin D sources **(Hollis and Wagner, 2004).**

1.4. Level of Vitamin D in adult serum

Although 1, 25$(OH)_2$D is the biologically active form of vitamin D, its half-life is less than 4 hours. In fact, 1, 25$(OH)_2$D may remain normal or even increase in vitamin D-deficient states***(Dlugos et al., 1995 ; Holick, 2004) ,*** so, It is universally accepted that the circulating level of 25-hydroxyvitamin D should be used as an indicator of vitamin D because it is easy to measure, has long half-life in circulation (approximately 2 or 3 weeks), and there is

correlation between its level and clinical disease states **(*Adams et al., 1982; Reichel et al., 1989; Wolpowitz and Gilchrest, 2006).***

Vitamin D deficiency is defined as a level of 25-hydroxyvitamin D of less than 20 ng per milliliter (50 nmol per litre) **(*Thomas et al., 1998; Holik et al., 2005; Lips et al., 2006; Michael, 2007*).** A level of 25-hydroxyvitamin D of 21 to 29 ng per millilitre (52 to 72 nmol per litre) is considered as an insufficiency of vitamin D, and sufficient vitamin D should reach a level of 30 ng per millilitre or greater ***(Dawson-hughes et al., 2005).***

On the other hand, vitamin D intoxication is extremely rare. Studies showed that doses of more than 50,000 IU per day, which raises 25-hydroxyvitamin D to more than 150 ng per milliliter, is associated with hypercalcemia and hyperphosphatemia**(Bouillon, 2001; Holick and *Garabedian., 2006; Holik, 2006).***

So, the serum values of 25-hydroxyvitamin D are interpreted as follows:

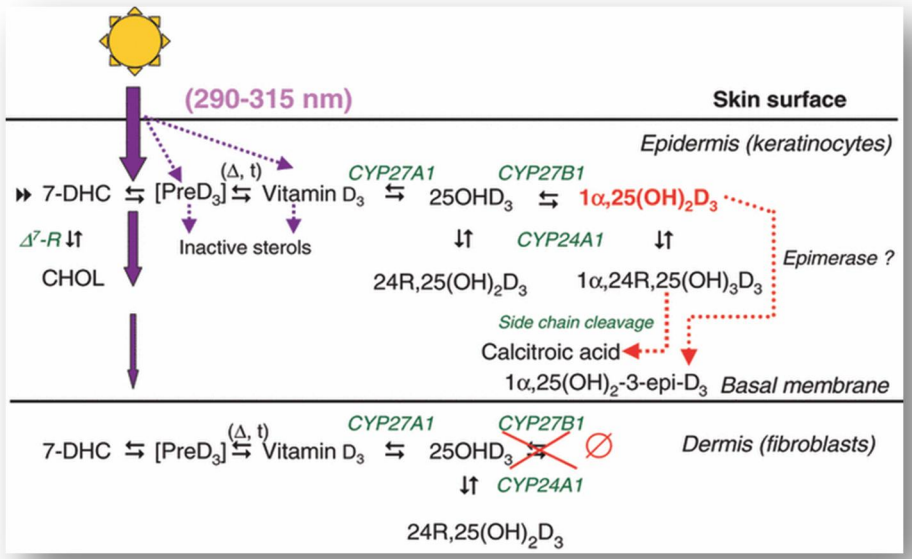
- <20 ng/mL (<50 nmol/L): deficient.
- 21–29 ng/mL (51–74 nmol/L): insufficient.

- >30 ng/mL (>75 nmol/L): sufficient**.**
- >150 ng/ml**:** intoxication ***(Holick and Chen, 2008).***

1.5. Metabolism of Vitamin D

1.5.1. Photochemical reactions in the skin

Human epidermal keratinocytes contain the complete machinery needed to produce the hormone 1 α ,25(OH)2D (calcitriol) from its initial precursor 7-dehydrocholesterol (7-DHC)***(fig.4).*** These cells also express the nuclear vitamin D receptor (VDR) that mediates the effects of this hormone on keratinocytes. Thus, it is reasonable to assume that calcitriol acts in an autocrine and paracrine manner in the epidermis ***(Lehmann, 2009).***



(Fig.4): Vitamin D pathway in epidermal keratinocytes (***Lehmann, 2009***).

7-dehydrocholesterol (7-DHC) is already stored in the basal and suprabasal layers of skin ***(Holick et al., 1980; Mac Laughlin et al., 1982),*** andis photolyzed to previtamin D (calciferol) during exposure to ultraviolet (UV) light ***(Prosser and Jones, 2004; Birlea et al., 2008).*** The photochemical reaction is maximum at wave length spectrum from 297 to 302 nm ***(Holick et al., 1980).*** So, vitamin D synthesis is almost confined to the UVB region (290 320 nm) and occurs at minimal rates in the UVA region (320 - 400 nm) ***(Wolpowitz and Gilchrest, 2006).***

If newly formed previtamin D continues to be irradiated, it is converted into additional products such as lumisterol 3, and tachysterol 3 that do not possess vitamin D activity any more , i.e.:. Excessive sunlight exposure cannot cause vitamin D toxicity because UVB converts excess vitamin D to biologically inert isomers ***(Prosser and Jones, 2004; Birlea et al., 2008).***

1.5.2. Limiting factors of the cutaneous vitamin D synthesis

There is a biochemical equilibrium between 7-DHC and cholesterol adjusted by the activity of 7-DHC-D7-reductase in epidermal keratinocytes. Thereafter, the conversion of 7-DHC into previtamin D in the skin depends on several individual and environmental factors ***(Chen et al., 2007; Lehmann, 2009):***

1.5.2.1. The concentration of 7-dehydrocholesterol (7-DHC) in the skin. The 7-DHC level in normal human adult skin ranges between 1.9 and 75 μg/cm2 ***(Lehmann, 2009).*** Under normal physiological circumstances, human skin has ample quantities of 7-DHC available in the stratum spinosum and stratum basale and which are mainly regulated by the activity of the 7-DHC-D7-reductase that catalyzes the conversion of 7-DHC to cholesterol and vice versa ***(Bonjour et al., 1987),***

1.5.2.2. The energy of photons that – in turn - depends upon the wavelength of the ultraviolet rays,

1.5.2.3. Both the solar zenith angle (which is a function of latitude and season) and time of the day. Solar zenith means the distance between the sun and the earth**,**

1.5.2.4. Skin pigmentation which is determined by the concentration of melanin in the skin. Melanin, which absorbs UVB in the 290–320 nm range, functions as a light filter and, therefore, determines the proportion of the incident UVB that is actually able to penetrate the outer epidermal layers and arrive at the stratum basale and stratum spinosum ***(Chen et al., 2007).***

1.5.2.5. Use of sunscreens, which considerably suppresses photolysis of 7-DHC.

1.5.2.6. Temperature, which regulates the enzymatic conversion of previtamin D to vitamin D, and

1.5.2.7. Age, as there is an inverse relation between the epidermal concentrations of 7-DHC and the age ***(Feldman et al., 2005).***

1.5.3. Vitamin D activation and degradation pathways

After being synthesized, vitamin D is translocated to the circulation where it binds to vitamin D binding protein (DBP) to reach the peripheral tissues ***(Prosser and Jones, 2004; Birlea et al., 2008).***

- *Transport in Blood*

Vitamin D metabolites are transported in blood bound primarily to vitamin D binding protein (DBP) (85-88%) and albumin ***(Bikle et al., 1984; Cooke and Haddad, 1989).*** Vitamin D binding protein (DBP) concentrations are normally 4-8 times the concentration of the vitamin D metabolites, so that DBP is only about 2% saturated. DBP has high affinity for the vitamin D metabolites, such that under normal circumstances only approximately 0.03% of

25(OH)D and 24, 25(OH) $_2$D and 0.4% of 1, 25(OH)$_2$Dare free (***Bikle et al.,1984***; ***Bikle et al.,1986).*** Conditions such as liver disease and nephrotic syndrome, usually associated with reduced DBP and albumin levels will lead to a reduction in total 25(OH)D and 1, 25(OH)$_2$D levels, without necessarily affecting the free concentrations ***(Bikle et al., 1986).***

However, vitamin D intoxication can increase the degree of saturation sufficiently to increase the free concentrations of 1, 25(OH)$_2$D and so cause hypercalcemia without necessarily raising the total concentrations ***(Pettifor et al., 1995).***

Vitamin D binding protein (DBP) was originally known as group specific component (Gc-globulin) before its properties as a vitamin D transport protein became known. It has three common polymorphisms which are useful in population genetics but which do not appear to alter its function. DBP is a 58kDa protein with 458 amino acids that is homologous to albumin and α-fetoprotein (αFP). It is made primarily-but not exclusively-in the liver. Other sites include the kidney, testes, and fat ***(Horiuchi et al., 1977).*** DBP like other steroid hormone binding proteins is increased by oral (not transdermal) estrogens and