A Review of the Role of Vitamins in Psoriasis in Pregnancy

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Abstracts: Psoriasis is an immune mediated chronic inflammatory disorder. Psoriasis treatment regimen is an immune regulation and inhibition of the cell cycle to prevent hyper proliferation of keratinocytes. Psoriasis does not affect the reproductive ability of patients; however, psoriatic women in reproductive period should be aware of the side effects of psoriatic medication. Understanding the molecular mechanisms beyond Psoriasis is crucial in developing effective treatment options for Psoriasis and preventing birth defects such as spontaneous abortions, intermittent fetal bradycardia, malformations and miscarriages.

Vitamin A and vitamin D are the skin hormones that regulate the cell cycle of the keratinocytes. Vitamin A and D deliveries are extensively used in psoriasis treatment. Vitamin A is important for neuronal development; however, excessive use of vitamin A is teratogenic. Vitamin D is useful for Psoriasis treatment and is required for bone integrity. Vitamin D is also important for women's fertility. Both vitamin A and vitamin D play a pleiotropic role in metabolism by regulating different gene expressions. Thus, the use of the vitamins or their derivatives in psoriasis treatment is vital for the fetus development. In this review we focus on the vitamin A and D metabolism, particularly molecular and genetic aspects of psoriasis treatment during pregnancy.

Keywords: Psoriasis, Pregnancy, Vitamin D, Vitamin A, Retinoid.

INTRODUCTION

Psoriasis is a hyper-proliferative, relapsing inflammatory dermatosis with strong genetic susceptibility and multifactorial etiology [1]. Pathogenesis of Psoriasis is still unclear; however, the gene knock-in and knock-out studies are helpful in clarifying pathogenesis of psoriasis [2]. Several genome and epigenome wide association studies have focused on dozens of genes in their attempts to find out the immune mediated mechanisms of psoriasis [3-5]. Understanding the molecular mechanisms beyond psoriasis is crucial for the development of the effective treatment options of the disease. Psoriasis never affects the fertility of patients; however, psoriatic women in childbearing period must be aware of the side effects the medication has on a fetal growth.

Histologically, psoriasis is defined as an abnormal differentiation and proliferation of keratinocytes, infiltration of the T cells, dendritic cells, macrophages, neutrophils and neoangiogenesis. Keratinocytes are the specialized epithelial cells that undergo a well-defined differentiation cycle. Keratinocytes turnover from stem cells to mature keratinocyte takes 13 days; however, in psoriatic patients the turnover time of epidermal keratinocytes is shorter, between 1 and 3 days [6]. Proliferation of the keratinocyte occurs at the bottom of the stratum basal and during the differentiation process the keratiocytes move up to stratum corneum. From the molecular standpoint, the differentiation of the keratinocytes depends on several factors, such as level of calcium, vitamin A and vitamin D [7-11]. The concentration of the calcium, vitamin A and vitamin D vary in different layers. Calcium ions gradient is important for keratinocyte proliferation and differentiation of keratinocytes [11-12]. Furthermore, calcium concentration plays a major role in differentiation as well as migration of keratinocytes. Vitamin A and D are accepted as skin hormones because of the role they play in growth, differentiation and reproduction of skin cells by regulating gene expression [14, 15]. Vitamin D is an important regulator because of its ligand modulated transcription activity in steroid, thyroid, and retinoic acid genes [13].

Vitamin A Metabolism and Skin Homeostasis

Vitamin A is a fat soluble molecule that has a function in metabolic and physiologic activities. Animal fats (especially fish oil), yellow and green vegetables are the major sources of vitamin A. The body takes 75% of its vitamin A needs from retinyl esters (egg, liver, milk etc) and 25% from carotenoid (vegetables). Digested Vitamin A is transported to enterocytes by chylomicron transport, and then to hepatocytes through the lymphatic system. Digested retinyl esters are stored in the liver until they are released into the blood

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circulation system. Retinol, the hydrolyzed form of retinyl esters, is a molecule with low solubility and chemical stability in aqueous solutions; thus, retinol requires binding to retinol-binding protein (RBP). The cellular import of retinol-RBP complex occurs in specific transmembrane receptors (stimulated by retinoic acid –STRA6).

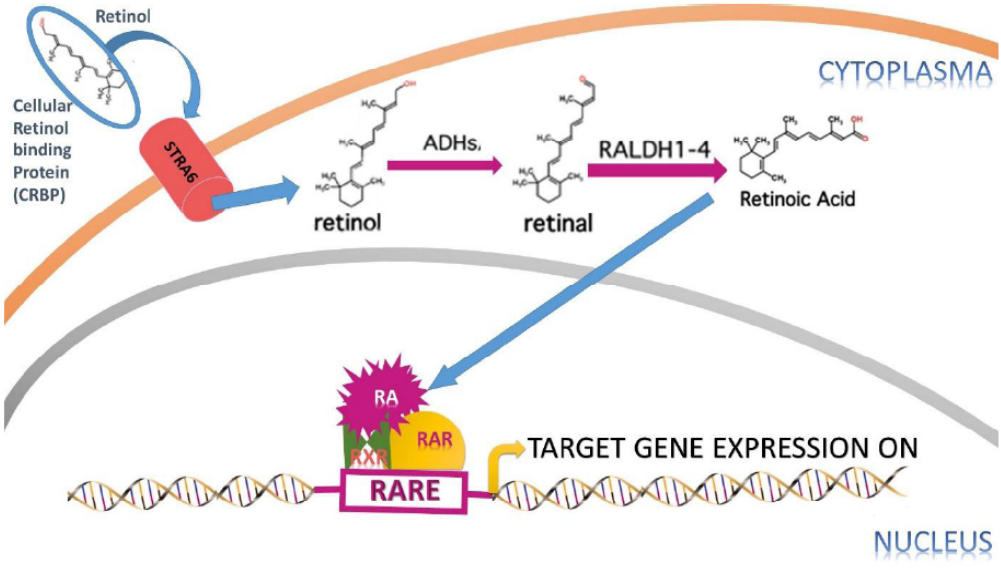
Retinoids (vitamin A and its derivatives) play an important role in transforming immature keratinocytes to mature form [16]. Retinoids represent its biologic function by binding to nuclear retinoic acid receptors (RAR) and retinoid-X-receptors (RXR). Retinoid mediated gene transcription are activated through binding of the RAR/RXR heterodimers or RXR/RXR homodimers complexes to retinoic acid responsive elements (RARE) in promotor region of the target genes; thus, this affects gene expression level upon ligand binding [17].

Previous studies have confirmed that synthetic trans-retinoic acid analogs decrease the expression of keratins 5, 6, 14, and 17 and increase the expression of keratins 13 and 19 [18]. Retinoids are widely used in dermatopharmacology because of their regulatory role in keratinocyte proliferation, epidermal differentiation and keratinization [8, 19]. Etretinate (Tigason, Tegison) and its active metabolite acitretin (Neotigason, Soriatane) are the retinoid acid derivatives that are used in dermatopharmacology.

Vitamin A and Management of Pregnancy in Psoriatic Women

Previous studies have shown that acitretin regulates T-helper (Th)1 and Th17 cells, which makes this and effective treatment in psoriasis. [20-21]. Psoriatic epidermal hyperplasia is a result of an imbalanced Th1/Th2 differentiation ratio. Psoriasis is a Th1 dominant condition, however, during pregnancy a temporarily switch to a Th2 system occurs and this prevents Th1 response; as a result, psoriasis improves during pregnancy [22]. Acitretin is an oral retinoid, which has various side effects, such as teratogenicity, cheilitis, xerosis, dyslipidemia, and photosensitivity [23]. Fetal abnormalities that occur due to oral use of retinoids include craniofacial, musculoskeletal and central nervous system anomalies [24-25]. Topical medications and phototherapy should be preferred instead of retinoids for female psoriatic patients with reproductive potential.

Patients with resistant skin psoriasis require systemic treatments, such as cyclosporine A, methotrexate, retinoids and biologic agents. Because of the more effective pharmacokinetic profile Acitretin is preferred even if patients are not responsive to other therapies [22, 26-28]. The previous report has shown that etretinate causes spontaneous abortions 2.75 and 3.2 years after discontinued use of medication. However, no complication occurred in women or babies 1, 3 and 5 years later after discontinued use of



*RBP (retinol binding proteins). STRA6 (stimulated by retinoic acid 6). CRBP (cellular retinol binding proteins). ADH (alcohol dehydrogenases). RDH (retinol dehydrogenases). RALDH (retinaldehyde dehydrogenases). RA (retinoic acid). CRABP (cellular retinoic acid binding proteins). RAR (retinoic acid receptors). RXR (retinoid X receptors). RARE (retinoic acid response element).

Figure 1: An overview of the retinoic acid pathway is represented.

etretinate [29]. Nijhof *et al.* [30] have shown that use of acitretin caused intermittent fetal bradycardia. The overdose of retinoic acid intake increased the risk of miscarriage. Thus, dermatologists should be performing pregnancy tests before applying acitretin treatment. Also, oral contraceptive drugs must be used along with acitretin. The predominant view is that pregnancy should be planned 2 years after discontinued use of acitretin [25].

The retinoic acids are required to arrange patterning and differentiation of neural development. However, an overdose of retinoic acid causes anomalies, such as neural tube defect(NTD) because of its effects on retinoic acid signaling and chromatin structure remodeling [31, 32]. Retinoic acids (RA) and thyroid hormones (TH) share common receptors (RXR) and bind to hormone-response elements (HREs); thus, there is a cross-talk between these hormone molecules [32]. The recent experiment has shown that the mouse fetuses that were exposed to an overdose of RA ectopically suppress TH signaling and spinal NTDs [32]. Retinoic signaling pathway is capable of changing cellular membrane permeability in human keratinocytes, as well as in amniotic environment, by regulating aquaporin (AQP) gene expressions [33-34]. All-trans retinoic acid have effects on trans-membrane flow of water and glycerol; thus, limitation of retinoic acid use is important in preventing adiposity and insulin resistance in fetus because of its secondary effect on fetal glucose and energy metabolisms [34-35].

There is also an increased risk of miscarriage. Therefore, psoriatic women in childbearing age should be informed about teratogenic effects of acitretin before the treatment is applied [36, 37]. The psoriatic women who use acitretin for psoriasis treatment must be informed before and during gestation period.

Vitamin D Metabolism and Skin Homeostasis

Bioactive form of vitamin D (1,25-dihydroxycholecalciferol) is a steroid hormone that has a pleiotropic role in metabolism by regulating different gene expression [9, 38]. Vitamin D production and catabolism occurs only in keratinocytes. Vitamin D is synthesized as a prohormone (7-dehydrocholesterol) and enters the blood circulation system through the skin or the lymph. Inactive form of vitamin D (pre-vitamin D3) is converted into circulating form (25-hydroxy (25-OH) vitamin D) in liver, then metabolically active form (1,25 dihydroxyvitamin D 1-25) is synthesized in kidneys [39]. The current literature shows that melanin pigments controls vitamin D3 synthesis [40-41]. Although the serum level of the vitamin D does not differ in albinism, genetic variations in genes involved in skin pigmentation (EXOC2, TYR,

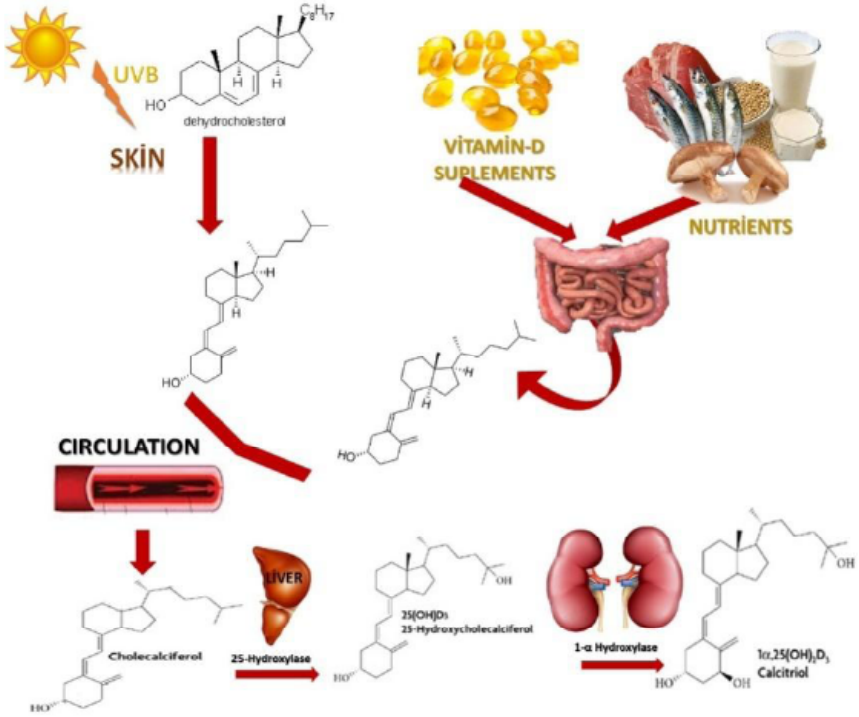


Figure 2: Vitamin D metabolism and transportation in the body.

TYRP1, and DCT) affect the 25(OH)D serum concentration [42].

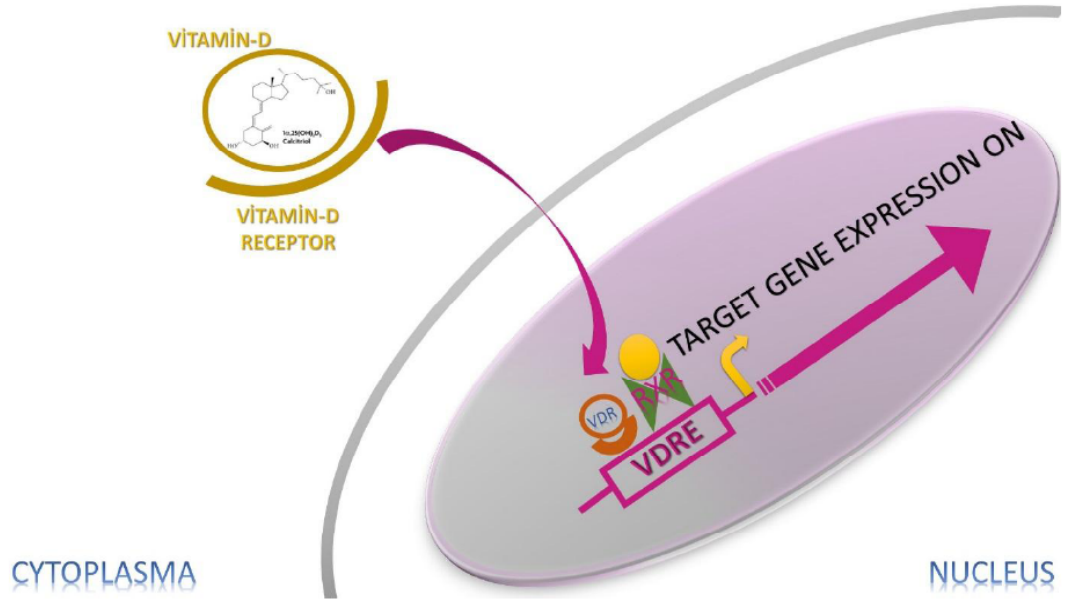
Vitamin D not only regulates mineral homeostasis (calcium and phosphate) and bone integrity, but also affects growth and differentiation of the cells [14]. Vitamin D is linked to several dermatological diseases such as atopic dermatitis, psoriasis, vitiligo, rosacea, skin malignancy because of its regulatory role in keratinocyte proliferation [43-49]. Active form of vitamin D regulates the balance between T helper 1(Th1) and Th2 cells. Calcipotriol (Psorcutan) is a topical form of active vitamin D analog used for the treatment of mild psoriasis because of its regulatory role in skin homeostasis. Vitamin D deficiency and genetic variations in vitamin D metabolism disrupt skin homeostasis. Thus, vitamin D supplements, topical vitamin D analogs and phototherapy are considered to be effective and safe methods for treating skin diseases. UVB phototherapy can be used in treating skin disease (psoriasis, eczema, vitiligo and morfea) because of its effects in converting 7-dehydrocholesterol to pre-vitamin D_3 [50].

When activated vitamin D binds with its heterodimeric intracellular receptor protein [vitamin D receptor/retinoic X receptor (VDR/RXR)], with the help of its co-regulatory proteins, this complex becomes capable of binding vitamin D responsive elements (VDRE) in specific DNA sequences [38] and then starts regulating several cellular metabolisms. This stimulation activates the expression of target genes. The VDR receptors are located in endothelial, intestinal, pancreatic, hemopoietic, cardiac and skeletal muscle cells, T and B lymphocytes, macrophages, mast cells, NK cells and Tregs [51-54]

Although vitamin D has effects on epidermopoiesis and melanin pigmentation [55]), no significant association between serum 25(OH)D level and albinism were found[56]. In fact, not only vitamin D level in the circulation, but also vitamin D receptor polymorphism have been associated with different diseases [57-58]. The further studies may show that the main reason for the skin disease is the genetic variation in vitamin D metabolism, rather than vitamin D deficiency. As an example, the association between atopic dermatitis (AD) severity and vitamin deficiency is contradictory. Serum vitamin D concentrations were not significantly related to AD severity in different populations [59, 60]. Vitamin D receptor polymorphism is associated with AD susceptibility [61-62].

Vitamin D and Management of Pregnancy in Psoriatic Women

Recent studies have shown that vitamin D is associated with many different diseases, including obesity and cancer [63-69]. Vitamin D has effects on *in vitro* fertilization (IVF), insulin resistance (IR), hyperandrogenism, endometriosis and polycystic ovary syndrome (PCOS) [66, 70-71]. The current literature



*VDR (Vitamin D Receptor), RXR (retinoid X receptors). VDRE (vitamin D response element)

Figure 3: An overview of the vitamin D action on target genes is presented.

discusses the relationship between vitamin D and female and male fertility [72-74]. Although Somigliana et al. [75] have been speculating on the lack of relationship between Serum Levels of 25-Hydroxyvitamin D and fertility, the prevalence of vitamin D deficiency in infertile women was extremely high in a German retrospective study [76]. Vitamin D deficiency in pregnant women increases the risk of gallbladder (GB) stasis [77]. Vitamin D is crucial in placental function and fetal growth [78], thus maternal vitamin D deficiency affects fetal and neonatal health [79, 80]. Hypovitaminosis D is a common problem in later stages of pregnancy and their newborns, as a result, vitamin D supplementation and sun-bathing is important for pregnant women [80, 81]. Fetal growth restriction (FGR) is a serious growth condition with high morbidity and mortality rate and affects 5% of all pregnancies. FGR is referred as poor growth of the fetus, hence fetus is smaller than genetically determined potential size. Management and prevention of the FGR can be achieved by supplementing Vitamin D [78]. The recent study has shown that Vdr gene ablation has an effect on fetal gene expression, yet Wilson et al. [82] have demonstrated that the effect of Vdr gene ablation can be tolerated by maternal system and has limited effects on placental morphology and function. To summarize, vitamin D is important for both maternal and fetal health, therefore, maternal supply of vitamin D and VDR signaling are essential for a successful pregnancy.

DISCUSSION AND CONCLUSION

Psoriasis is a disease that does not affect fertility of the patients. Symptoms of psoriasis can be noticed in early adult life. During pregnancy period severity of the psoriasis changes because of hormonal change. Thus, effective, affordable and safe treatment is required to ensure fetal growth and development. Vitamin D and vitamin A derivatives are widely used in psoriasis treatment, because both of them are capable of regulating gene expression by binding responsive elements on the genes. As a result, excessive vitamin or derivatives intake triggers up regulation or down regulation of the genes and causes fetal abnormalities during pregnancy. Thus, dermatologists should inform women in reproductive period about the teratogenic effects of vitamin A derivatives. Also, dermatologist must be careful about vitamin derivates and should work closely with obstetric and gynecologist during pregnancy.

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