Introduction

Vitamin D receptor expression is found in monocytes, stimulated macrophages, dendritic cells, natural killer cells, and T and B cells. Thus, VDR activation elicits potent immune-modulatory effects, affects levels of inflammatory cytokines, and plays a key role in both the innate and adaptive immune systems ***(Wilkinson et al., 2000).***

Vitamin D deficiency leads to immune dysregulation and proposed as an underlying pathogenic mechanism of infections, associated with increased markers of systemic inflammation and multi-organ failure. ***(Hewison et al.,2004 & Jeng et al ., 2009).***

Low maternal vitamin D levels during pregnancy linked to various health outcomes in the offspring, including higher incidence of abortion, low birth weight, neonatal hypocalcemia, impaired development, immune dysfunction ***(Tavakoli et al., 2011 & Brown et al., 2004).***

A positive correlation exists between maternal and infant plasma 25(OH)D concentrations within 72 hours after birth, this may be explained by the ability of serum 25(OH) D to cross the placenta ***(Lee et al.,2007).***

The association of 25(OH)D deficiency and infections is likely due to the pleiotropic effects of 25(OH)D on human immunity, including T-cell proliferation, immunoglobulin class-switching, and cytokine release , also enhances signaling of the innate immune system to increase the production of antimicrobial peptides (AMP) ***(Mora et al.,2008 & wang et al.,2004).***

Aim of work

The primary aim is to study the effect on neonatal vitamin D level on early onset neonatal sepsis in full term neonate.

The secondary aim is to study the correlation of maternal vitamin D levels to neonatal vitamin D levels

Chapter (1)
Vitamin D

Vitamin D structure, synthesis and sources:

Vitamin D is a steroidal pro-hormone, the active type which plays a significant role in absorption of calcium and phosphate, it reaches the body through skin synthesis via ultraviolet rays when the sun exposure is adequate and can be ingested through food, through influencing the absorption of calcium in the intestinal tissues and other effects on bone and other tissues of the body, the metabolites of this vitamin have key roles in regulating the metabolism of minerals (figure 1) ***(Mulligan et al., 2010).***

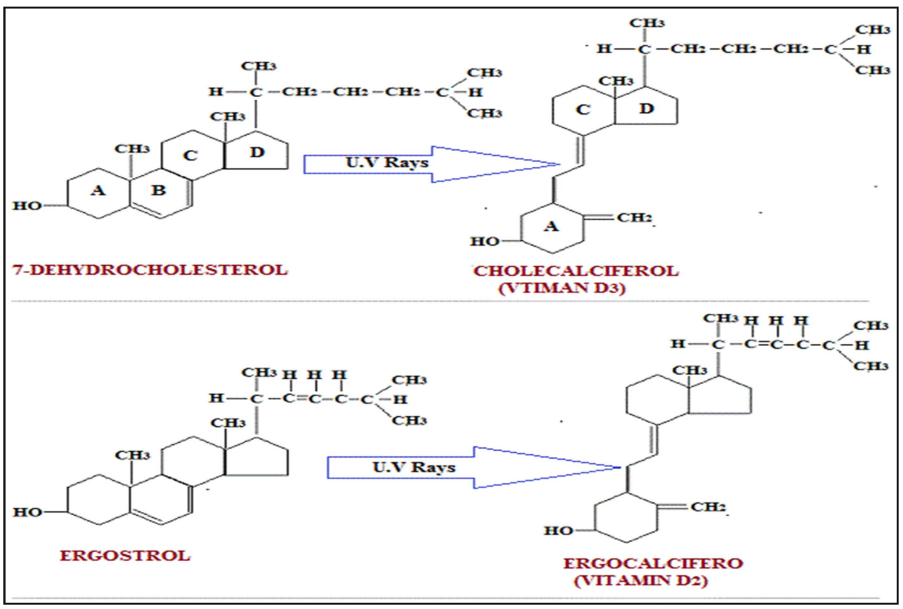

Figure (1): The structure of the active vitamin D hormone

Vitamin D is obtained from limited dietary sources or photochemical and thermal conversion of 7-dehydrocholesterolin skin, 'Vitamin D' refers collectively to vitamin D3 (cholecalciferol), derived from metabolism of cholesterol and related vitamin D2 (ergocalciferol), derived from the fungal steroid ergosterol ***(Tavera-Mendoza and white, 2007).***

Near-exclusive breastfeeding for 6 months leads to maternal calcium loss 4 times higher than in pregnancy because lactation can require 150–300mg Ca. Kg ***(Dawson et al., 2005).***

The lactation-induced adaptations to maternal calcium homeostasis are illustrated in (Figure 2). Parathyroid hormone-related protein (PTHrP) produced by the lactating breast in combination with low estradiol concentrations appears to drive the main physiologic adaptation to meet the calcium demands of lactation ***(Wysolmerski, 2007).***

PTHrP enters the blood stream and combines with systemically low estradiol concentrations to markedly up-regulate bone resorption. Increased bone resorption releases calcium and phosphate into the bloodstream, which then

reaches the breast ducts and is actively pumped into the breast milk ***(Dawson et al., 2005).***

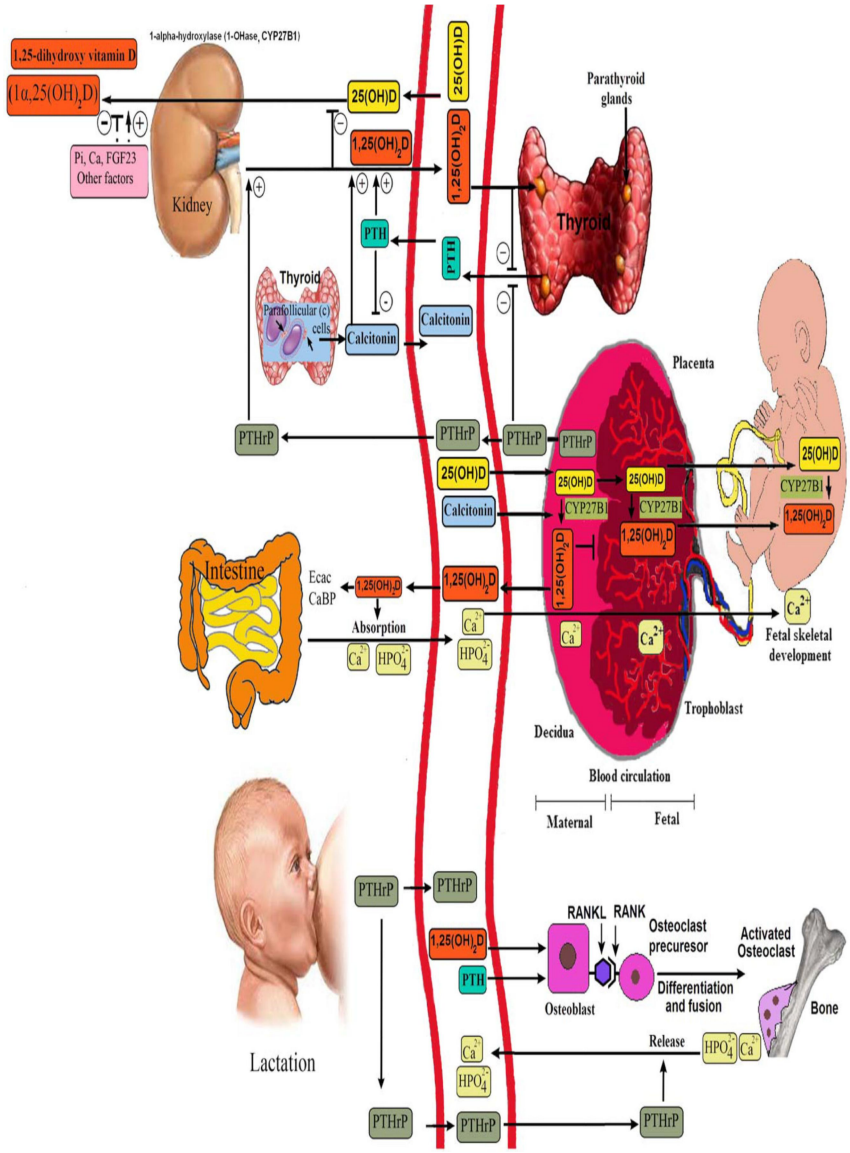

Figure (2): Vitamin D metabolism during pregnancy and lactation.

Pathway of vitamin D production

Dietary or cutaneous vitamin D must undergo two modifications to become biologically active. Hepatic hydroxylation catalyzed by CYP27A1, CYP2R1 and possibly other enzymes generates 25-hydroxyvitamin D which has a half-life of several weeks and represents the major circulating metabolite and measure of vitamin D status,25D is converted by 1a-hydroxylation catalyzed by CYP27B1 into the hormonally active 1,25-dihydroxyvitaminD (1,25D) (Figure 3) ***(Holick, 2007).***

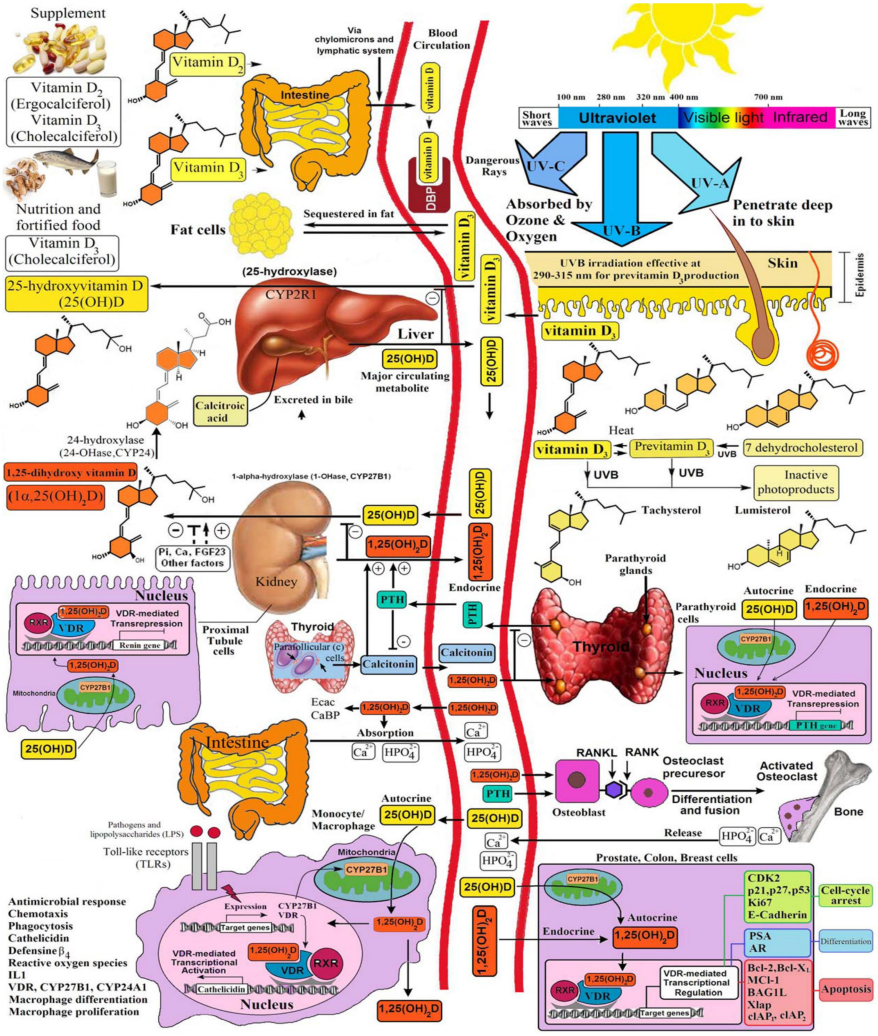

Figure (3): representation of the synthesis and metabolism of vitamin D

1,25D is produced locally in many tissues for function in an intracrine or paracrine manner. In a negative feedback loop, 1,25D strongly induces expression of the gene encoding CYP24, the enzyme that initiates catabolic degradation by catalyzing hydroxylation of 25D or 1,25D at

the 24 position to produce biologically inactive metabolites ***(Hewison et al., 2007).***

Relationship between maternal 25 (OH) D concentration and infant outcomes:

During pregnancy, fundamental changes occur in calcium and vitamin D metabolism ***(Abbasian et al., 2016).***

Requirement for calcium increases in the third trimester of pregnancy so that in the final stages of pregnancy, about 30g of the calcium for the fetal skeleton is created from the maternal skeleton and through hormonal intervention so it is vital to receive adequate vitamin D and calcium during the pregnancy for the fetal homeostasis, bone growth and mineral development ***(Cavalier et al., 2008).***

Maternal vitamin D status is responsible for fetal and newborn vitamin D status because a fetus receives all vitamin D support from the mother. Maternal 25 (OH) D readily crosses the placenta and as early as 24 weeks gestation is metabolized to 1, 25 (OH) 2D by the fetal kidneys for endocrine action and by other tissues for paracrine action ***(Wagner et al., 2010).***

The optimal vitamin D concentration in pregnancy and newborns is still disputed and unknown ***(Marshall et al., 2013).***

Maternal plasma 25 (OH) D concentration during pregnancy is significantly correlated with cord blood plasma 25(OH)D ***(Lee et al.,2007).***

Cord blood concentration being from two-thirds to equal maternal concentrations, this is explained by the ability of serum 25(OH) D to cross the placenta. In contrast, maternal serum 1, 25(OH) 2D does not cross the placenta and does not contribute to the newborn's serum 1, 25(OH) 2D levels ***(Baeke et al., 2010).***

Role of Vitamin D in Neonatal Immune Function **(figure 4,5)**

Immaturity in adaptive immune functions at the time of birth and during infancy increases the neonate's dependence on the innate immune system to fight infections ***(Walker et al., 2011).***

Vitamin D receptor (VDR) and the vitamin D activating enzyme 1-α-hydroxylase (CYP27B1) are expressed in many cell types which are not involved in bone and mineral metabolism, such as intestine, pancreas, prostate and cells of the immune system including in T lymphocytes, neutrophils

and antigen presenting cells such as macrophages and dendritic cells and that 1,25D signaling modulates both innate and adaptive immune responses ***(Battault et al., 2013).***

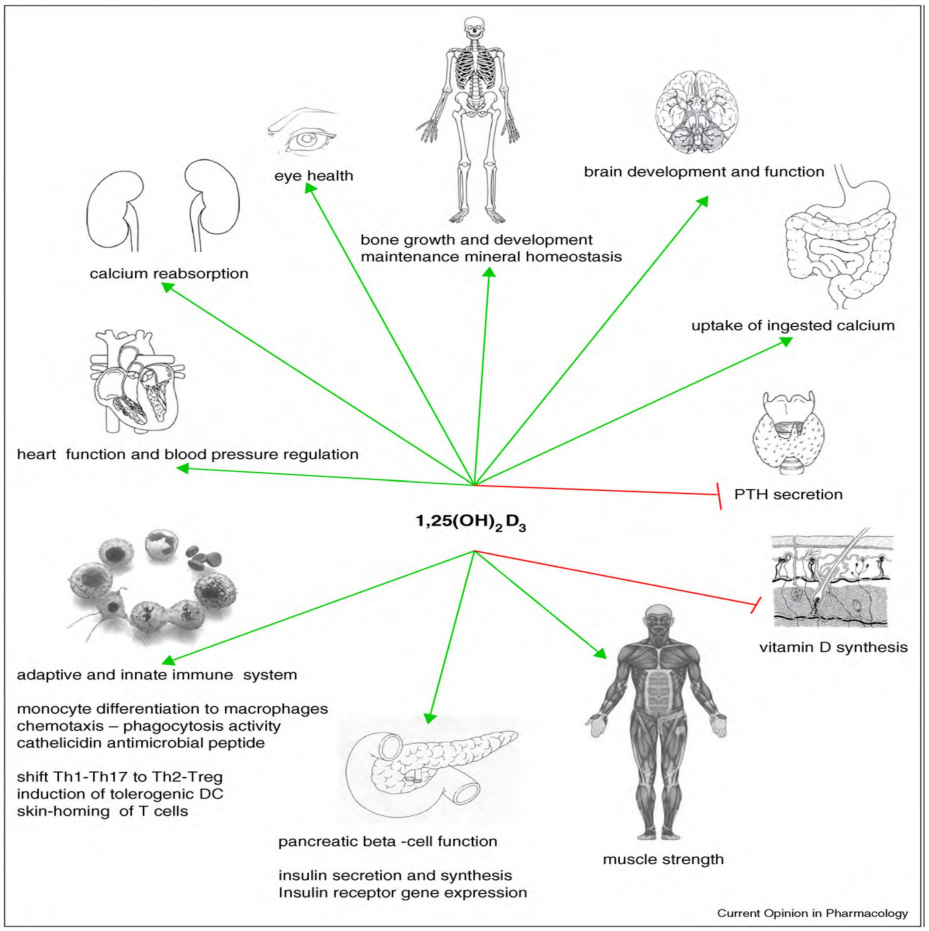

Figure (4): Role of VDR in many cell types

The VDR binds 1,25(OH)2D3 with a much greater affinity than 25(OH)D3 .Vitamin D also modulates the expression of Toll-like receptors (TLRs) and the co-receptor

CD14 on important innate immune cells promotes the conversion of 25 (OH) D3 to the active form (1,25 (OH) 2D3) and induces production of anti-microbial peptides, such as cathelicidin which inhibit the growth of both gram positive and gram negative bacteria ***(Ojaimi et al., 2013).***

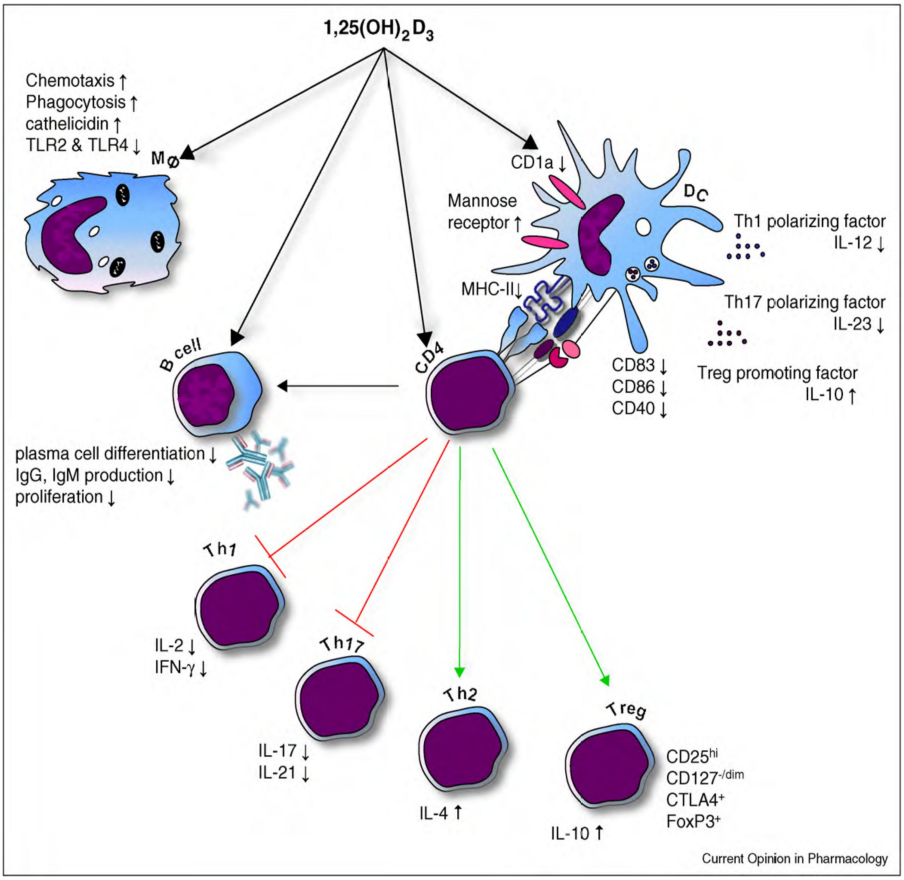

Figure (5): Role of vitamin in immune function

Vitamin D signaling in T cells:

1,25D signaling regulates the function and phenotype of dendritic cells (the most potent of the antigen presenting cells) enhances dendritic cell tolerogenicity which promotes the production and function of T regulatory cells (critical mediators of immune system tolerance) also acts directly on T lymphocytes to inhibit their proliferation ***(Adorini, 2009).***

1,25 (OH) signaling represses the transcription of gene encoding key T helper (Th1) pro-inflammatory cytokines, such as interferon -γ (IFN-γ) and interleukins 17 & 21 ***(Baeke,2010).***

The effects of 1,25D on T cell phenotypes would be consistent with the increasing evidence that vitamin D sufficiency acts to suppress T cell-driven autoimmune disease, several epidemiological studies have reported inverse correlations between circulating 25D levels and risk of other autoimmune conditions such as multiple sclerosis, rheumatoid arthritis, and type-1 diabetes ***(Gorman et al., 2010).***

1,25D signaling regulates T cell antigen receptor function. Engagement of the T cell antigen receptor on naïve human T cells led to p38 MAP kinase-dependent stimulation

of VDR expression, which in turn strongly induced expression of phospholipase C-γ1, a cofactor of the classical T cell antigen receptor signaling pathway within 48 h of initial T cell receptor stimulation, that 48 h lag might be an evolutionarily conserved mechanism to prevent explosive T cell proliferation in the presence of antigen ***(Jeffery et al., 2009).***

1,25D signaling enhances innate immune responses to infection, the lag in T cell activation would represent a coordinated strategy to decrease the potential for T cell-driven immune-pathology ***(Solomon, 2010).***

Regulation of Dendritic Cell Function by Vitamin D: (figure 6)

Dendritic cells specialize in capturing, processing and presenting antigens to the adaptive immune system. Dendritic cells express lymphocyte co-stimulatory molecules then migrate to lymphoid organs and secrete cytokines for the regulation of immune responses ***(Boltjes, 2014).***

During DC-differentiation, APCs down-regulate the monocytic marker CD14 while up-regulating the DC marker CD1a.Addition of 1,25(OH)2D3 completely inhibited the differentiation of CD1a+ DCs, while sustaining the expression of monocytic markers Moreover, activation of

VDR signaling pathways also inhibited DC-maturation as evidenced by levels of DC markers, MHC-class II, co-stimulatory molecules (CD40, CD80, and CD86), and other maturation induced surface markers ***(Pedersen et al., 2009)***.

1,25 (OH) 2D3 may play an important role in DC binding and capturing foreign antigens at the initiation of immune response, since this hormone up-regulated mannose receptor expression (a molecule involved in antigen uptake) and this correlated with an enhanced endocytotic capacity, also modulates DC-derived cytokine and chemokine expression by inhibiting the production of IL-12 and IL-23, enhancing the release of IL-10 and the chemokine MIP-3a ***(Mosser, 2008).***

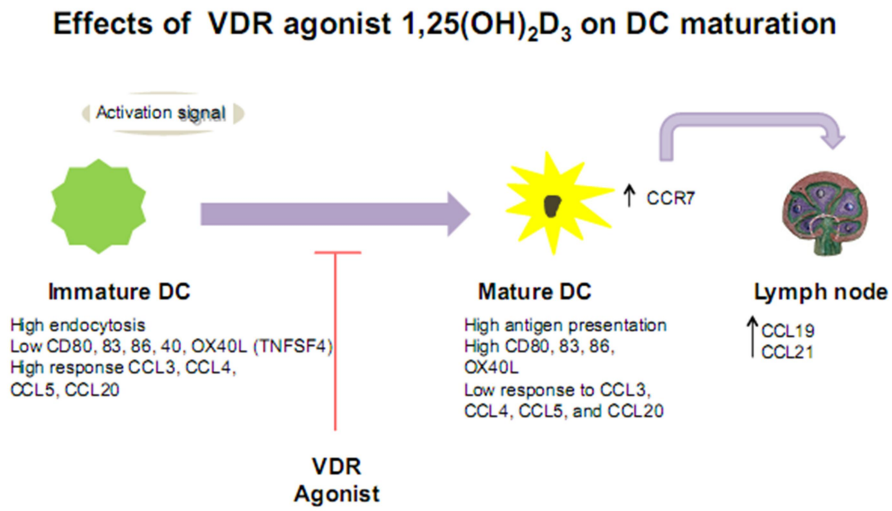

Figure (6): Overview of vitamin D on dendritic cell function