Section A -Research paper

Vitamin D Status among Neonates with Pneumonia

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Abstract:

The vital role of vitamin D in immune system function and regulation since 1, 25 dihydroxy vitamin D can promote the innate immature response to the pathogen. Few studies regarding the link between vitamin D and pulmonary infections among neonates have been found**.**

Keywords: Vitamin D, Neonates, Pneumonia, Inflammatory.

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Introduction:

Vitamin D is a fat-soluble vitamin which belongs to the steroid compounds. The largest source of vitamin D in adults is synthesis from solar radiation; half an hour of sunlight delivers 50 000 iu of vitamin D with white-complexioned skin. Dietary ingestion of vitamin D makes a relatively small contribution to overall vitamin D status as there is little vitamin D that presents naturally in the food supply found in fish-liver oils, fatty fish, mushrooms, egg yolks, and liver. Melanin absorbs ultraviolet B (UVB) from sunlight and lowers cholecalciferol production by at least 90%. Dietary vitamin D is absorbed from the intestine and circulates in plasma bound to vitamin D binding proteins **(1).**

Several forms of Vit D have been discovered. The two major forms are Vit D2 or ergocalciferol, and Vit D3 or cholecalciferol. These are known collectively as calciferol **(2).**

Vitamin D3 is three times more effective than vitamin D2 in increasing vitamin D concentrations and maintaining those levels for a prolonged time **(3).**

Production in the skin:

It is synthesized in the epidermis of the skin after UVB exposure or ingested in diet and is transported to the liver by vitamin D-binding protein where it is hydroxylated in the 25 position to yield 25 hydroxyl vitamin D (calcidiol or calcifediol) **(1).**

Production is greatest in the stratum basale and stratum spinosum. Vit D3 is made in the skin when 7-dehydrocholesterol

absorbs UVB ultraviolet light at wavelengths between 270–300 nm **(4).**

The primary source of Vit D is UVB irradiation from the sun. From spring until autumn, 15 minutes of sunlight exposure to face, arms, and hands is enough to maintain adequate levels of Vit D (**5).**

Synthesis mechanism:

Vit D itself is biologically inactive, and it must be metabolized to its biologically active forms. After it is consumed in the diet or synthesized in the epidermis of skin, Vit D enters the circulation and is transported to the liver. In the liver, Vit D is hydroxylated to form 25(OH)D. Increased exposure to sunlight or increased dietary intake of Vit D increases serum levels of 25(OH)D, making the serum 25(OH)D concentration a useful indicator of Vit D nutritional status. In the kidney, the 25(OH)D3-1-hydroxylase enzyme catalyzes a second hydroxylation of 25(OH)D, resulting in the formation of 1,25-dihydroxyVit D .the most potent form of Vit D. Most of the physiological effects of Vit D in the body are related to the activity of 1,25-dihydroxy vit D (**6**).

25-hydroxyvitamin D constitutes the major circulating form of vitamin D, and it is hydroxylated by the enzyme 1-alpha hydroxylase in the kidney to yield 1,25dihydroxy vitamin D, which is the active form of vitamin D, and this metabolite is responsible for the effect of vitamin D on calcium and phosphorus metabolism, bone health, and regulation of parathyroid function **(1).**

Multiple factors influence the synthesis of vitamin D through the skin such as duration of sun exposure, altitude, season, time of day, pigmentation of the skin, sunscreen use, behavioral habits and diet. The reference values for vitamin D concentrations were recently reviewed, being considered as vitamin D insufficiency values below 20 ng/mL **(7).**

Mechanism of action:

Following the final converting step in the kidney, calcitriol (1,25-dihydroxy vit D) (the physiologically active form of Vit D) is released into the circulation. By binding to Vit D-binding protein (VDBP), a carrier protein in the plasma, calcitriol is transported to various target organs (**4**).

Calcitriol mediates its biological effects by binding to the Vit D receptor (VDR), which is principally located in the nuclei of target cells. The binding of calcitriol to the VDR allows the VDR to act as a transcription factor that modulates the gene expression of transport proteins (such as TRPV6 and calbindin), which are involved in calcium absorption in the intestine .The VDRs belongs to the nuclear receptor superfamily of steroid/thyroid hormone receptors, and VDRs are expressed by cells in most organs, including the brain, heart, skin, gonads, prostate, and breast. **(8).**

VDR activation in the intestine, bone, kidney, and parathyroid gland cells leads to the maintenance of calcium and phosphorus levels in the blood (with the assistance of parathyroid hormone and calcitonin) and to the maintenance of bone content (**5).**

The VDR is known to be involved in cell proliferation and differentiation. Vit D also affects the immune system, and VDRs

are expressed in several white blood cells, including monocytes and activated T and B cells **(5)**.

Adequate intake:

The American Academy of Pediatrics currently recommends 400 IU/day of Vit D for all infants, children, and adolescents .

The Recommended Dietary Allowance (RDA):

In 2011, the Food and Nutrition Board (FNB) of the Institute of Medicine set RDA based on the amount of Vit D needed for bone health. While the recommended intake was increased from the adequate intake level some experts feel that this level is still too low to result in sufficient 25(OH)D levels.

Table (1): The RDA for vit D is listed in the table below by life stage and gender-RDA for Vit D Set by the Institute of Medicine**(9)**

Life Stage	Age	Males mcg/day (IU/day)	Females mcg/day (IU/day)
Infants	0-6 months	10 mcg (400 IU) (AI)	10 mcg (400 IU) (AI)
Infants	6-12 months	10 mcg (400 IU) (AI)	10 mcg (400 IU) (AI)
Children	1-3 years	15 mcg (600 IU)	15 mcg (600 IU)
Children	4-8 years	15 mcg (600 IU)	15 mcg (600 IU)
Children	9-13 years	15 mcg (600 IU)	15 mcg (600 IU)
Breast-feeding	all ages	-	15 mcg (600 IU)

Dietary sources of Vit D include fish such as salmon (530 IU per 3.5 ounces), sardines (231 IU per 3.5 ounces), mackerel (213 IU per 3.5 ounces), and cod oil (400 IU per teaspoon**)**. Mushrooms are also high in Vit D. Foods that are enriched with Vit D include whole milk (100IU per 8 oz), orange juice (100IU per 8 oz), some cereals, and some yogurts (Jane ,2004). However, foods fortified with Vit D do not contain adequate levels to satisfy the daily recommended dosage (**10).**

Functions of vitamin D:

1-Calcium Homeostasis:

One of the major functions of Vit D is to maintain calcium homeostasis. The binding of Vit D to the Vit D receptor is necessary for calcium and phosphorus absorption. Vit D is required for intestinal calcium absorption and Vit D deficiency results in only 10-15% absorption of dietary calcium and 60% of phosphorous is absorbed (**11).**

When Vit D levels are adequate, absorption of dietary calcium increases to 40% while 80% of phosphorous is absorbed. A lack of Vit D results in increased parathyroid activity which increases osteoclasts, which break down bone, thus, increasing the risk for osteoporosis. **(12).**

2-Vit D and the Immune System:

VDR ligands have been shown to increase the activity of natural killer cells, and enhance the phagocytic activity of macrophages. (**13).**

VDRs are present on cells responsible for both the innate and adaptive immune response, including T cells, B cells, macrophages, and dendritic cells (**14).**

Vit D affects the expression of genes involved in an immune response; it increases the gene expression of cathelicidin, which kills bacteria, and CD14, which aids in the recognition of various pathogens (**14).**

Increased incidence of respiratory infection is linked to Vit D deficiency. Epidemiological studies indicate that people with low levels of Vit D are 40% more likely to have a respiratory infection. Additionally, asthma patients with low levels of Vit D are 5 times more likely to have a respiratory infection **(14).**

3-Vit D and Reproduction:

Some women having difficulty with ovulation may not have enough Vit D (**15).**

It activates an immune response in human placental tissue which can prevent infection from pathogenic bacteria such as staphylococcus, streptococcus, and *E. coli***(15).**

In addition, epidemiological studies have shown that 93% of women with bacterial vaginosis are deficient in Vit D(**16).**

4- Vit D and the Nervous System:

Vit D plays a critical role in brain development and function. Vit D receptors are broadly distributed throughout the embryonic and adult brain **(17).**

Moreover, Vit D regulates important neurotrophic factors in the brain such as nerve growth factor (NGF), which affect neuroplasticity and neurotransmission. Also, Vit D increases the expression of glial cell line-derived neurotrophic factor (GDNF), which inhibits the cell death of dopamenergic neurons in the substantia nigra, the degeneration of which is responsible for the symptoms of Parkinson's disease **(18).**

Vitamin D serum level testing:

Examination of plasma calcidiol is the most sensitive vitamin D level test. Calcidiol has a half life of 19-31 days and demonstrates the level of vitamin D acquired from food and synthesized in the skin for several weeks to months. The Endocrine Society found the normal level of calcidiol to be 30-100 ng/mL, with insufficiency occurs at 21-29 mg/mL, and deficiency occurs under 20 ng/mL**.** Severe deficiency is defined as a 25(OH)D level less than 10 ng/ml **(19).**

Vit D deficiency:

Vitamin D deficiency is usually defined as a 25(OH)D level <50 nmol/L (20 ng/ml) and vitamin D insufficiency as a 25(OH) D level of 50–72 nmol/L (20–29 ng/ml) **(20).**

Because an estimated one billion people worldwide suffer from vitamin D deficiency or insufficiency, vitamin D has become an vital focus of current medical research**(1).**

Vitamin D deficiency is common in northern Europe, especially in females with pigmented skin. Vitamin D deficiency is three times more common in the winter and spring if compared to the summer and autumn in the UK **(7).**

A cohort study conducted in Brazil evaluated the effect of vitamin D deficiency on neonatal outcomes of pregnant females with GDM. The authors identified that newborns of women with vitamin D deficiency had a significantly increased incidence of hospitalization in critical care units, hypoglycemia, and small size for gestational age. The incidence of prematurity, jaundice, and dystocia of the shoulder were not statistically significant among groups **(19).**

Risk Factors for Vit D Deficiency:

Exclusively breast-fed infants: Infants who are exclusively breast-fed and do not receive Vit D supplementation are at high risk of Vit D deficiency, particularly if they have dark skin and/or receive little sun exposure **(21).**

Dark skin: People with dark-colored skin synthesize less Vit D on exposure to sunlight than those with light-colored skin .The risk of Vit D deficiency is particularly high in dark-skinned people who live far from the equator. One U.S. study reported that 42% of African American women between 15 and 49 years of age were Vit D deficient compared to 4% of White women**(21).**

Aging: The elderly have reduced capacity to synthesize Vit D in skin when exposed to UVB radiation, and the elderly are more likely to stay indoors or use sunscreen, which blocks Vit D synthesis. Institutionalized adults who are not supplemented with Vit D are at extremely high risk of Vit D deficiency. Covering all exposed skin or using sunscreen whenever outside: Osteomalacia has been documented in women who cover all of their skin whenever they are outside for religious or cultural reasons .The application of sunscreen reduces production of Vit D by 95% **(22).**

Fat malabsorption syndromes: Cystic fibrosis and cholestatic liver disease impair the absorption of dietary Vit D.

Inflammatory bowel disease: People with inflammatory bowel disease like Crohn's disease appear to be at increased risk of Vit D deficiency, especially those who have had small bowel resections.

Obesity: Obesity increases the risk of Vit D deficiency. Once Vit D is synthesized in the skin or ingested, it is deposited in body fat stores, making it less bioavailable to people with large stores of body fat (**23).**

Effect of vitamin D deficiency:

1- Osteoporosis:

The elderly are particularly susceptible to osteoporosis and are frequently deficient in Vit D **(9).**

2- Rickets in Infants:

Severe Vit D deficiency also negatively affects children by adversely affecting bone

development and reducing minerialization, resulting in a condition known as rickets **(9).**

Rickets is particularly common in children, and is a softening of the bones whicih leads to deformity and reduced bone tensile strength. It causes bowed legs, and knock-knees. Infants of African-American descent, and anyone whose skin contains a relatively large amount of melanin are at particular risk of rickets and/or Vit D deficiency because melanin acts as a filter that absorbs solar radiation (**24).**

3- Diabetes:

The World Health Organization estimates that 180 million people have diabetes worldwide Three-quarters of youth with type 1 diabetes are deficient in Vit D **(25).**

Children deficient in Vit D have an increased risk for developing type 1 diabetes, and one study found that children given Vit D supplement were found 30% less likely to develop type 1 diabetes than those who were not **(26).**

4-Obesity:

Vit D deficiency can promote unhealthy weight gain and stunt growth during puberty.Vit D levels are linked to the ability to successfully lose weight. For each 1 nanogram per ml increase of Vit D, subjects were able to lose a half a pound more than controls **(27).**

Cutaneously synthesized Vit D is stored in fat tissue and obese individuals have greater than 50% less bioavailability of Vit D compared to non-obese individuals **(27).**

5- Depression:

Depression is also correlated to Vit D deficiency. In an epidemiological study involving over 1000 adults, those with major or minor depression had significantly lower levels of Vit D. Vit D response elements are also located on two genes that regulate depression: the serotonin receptor and tryptophan hydroxylase. Therefore, Vit D has a direct physiological role in regulating depression . (**28).**

6-**Systemic Lupus Erythematosus:**

Vit D deficiency is also a risk factor for SLE, an autoimmune disease. Vit D supplementation ameliorated symptoms in a mouse model for SLE **(29).**

7-Rheumatoid Arthritis:

Rheumatoid arthritis is associated with insufficient levels of Vit D). Supplementation with a Vit D analogue results in symptomatic alleviation in 89% of patients with rheumatoid arthritis (**29).**

8- Inflammatory Bowel Disease:

Vit D is also associated with IBD; 50% of patients with IBD are deficient in Vit D Moreover, supplementation with Vit D ameliorate symptoms in a mouse model of IBD . **(30).**

9- Vit D and Cardiovascular Disease:

Vit D regulates renin, a hormone that is a critical modulator of blood pressure. Low serum levels of Vit D will activate the renin-angiostensin system, causing thickening of blood vessels . **(**31**).**

People with serum Vit D levels below 15 nanograms per ml are twice as likely to experience a heart attack or stroke **(32)**.

10- Vit D and Cancer:

Vit D also has been implicated in the prevention of cancer. Epidemiological studies demonstrate that a daily dose of 1500 IU of Vit D resulted in a 17% reduction of total cancer, a 29% reduction in cancer mortality, a 43% decrease risk of cancer of the digestive system as well as a 45% decrease in mortality **(33).**

11- Vit D and Cystic Fibrosis;

Vit D deficiency is prevalent among children with cystic fibrosis (CF). A distinguishing characteristic of CF is the inability to absorb nutrients resulting in malnutrition. Between 2003 and 2006, 86% of pediatric patients with CF were Vit D deficient (serum levels lower than 30 nanograms per milliliter). Adequate blood levels of Vit D were not achieved in most patients even at 3 times the recommended dose. It wasn't until the dose was raised to approximately 25 times the recommended dose (50,000 IU three times weekly) that adequate Vit D levels were maintained (**2).**

Vitamin D Toxicity:

Opposite to vitamin D receptor activator (VDRA), nutritional vitamin D compounds are unlikely to induce hypercalcemia using a normal regimen because its 1α-hydroxylase activation is regulated by PTH, FGF-23 and 24-hydroxylase. Therefore, a serum 25(OH)D level up to 100 ng/mL is considered safe. In the general population, daily vitamin D intakes >10,000 IU may be toxic because they lead to DBP saturation with an increase of free serum 25(OH)D. In addition, toxicity has been observed for higher dosages (>40,000 U/day) **(34).**

In healthy childern, sustained intake of 1250 micrograms/day (50,000 IU) can produce overt toxicity after several months those with certain medical conditions are far more sensitive to Vit D and develop hypercalcaemia in response to any increase in Vit D nutrition, while maternal hypercalcaemia during pregnancy may increase fetal sensitivity to effects of Vit D and lead to a syndrome of mental retardation and facial deformities (**22).**

For infants (birth to 12 months) the tolerable Upper Limit (maximum amount that can be tolerated without harm) is set at 25 micrograms/day (1000 IU). 1000 micrograms/day (40,000 IU) in infants has produced toxicity within 1 month. The U.S. Dietary Reference Intake Tolerable Upper Intake Level (upper limit) of Vit D for children and adults is set at 50 micrograms/day (2,000 IU). Vit D overdose causes hypercalcemia are; anorexia, nausea, and vomiting can occur, frequently followed by polyuria, polydipsia, weakness, nervousness, pruritus,. Proteinuria, urinary casts, azotemia, and metastatic calcification (especially in the kidneys) may develop and ultimately renal failure. Vit D toxicity is treated by discontinuing Vit D supplementation and restricting calcium intake. Kidney damage may be irreversible**(35).**

Exposure to sunlight for extended periods of time does not normally cause Vit D toxicity. This is because within about 20 minutes of ultraviolet exposure in light skinned individuals (3–6 times longer for pigmented skin) concentrations of Vit D precursors produced in the skin reach an equilibrium, and any further Vit D that is produced is degraded (**5).**

Vitamin D Status among Neonates with Pneumonia

In its most general form, pneumonia can be understood to refer to inflammation of the lungs that is brought on by an infectious pathogen that provokes a reaction that damages lung tissue. Pneumonia is responsible for roughly one in five deaths that occur among children aged five and older over the world. The etiological variables of pneumonia vary depending on the patient's age, the location of the infection (whether it was acquired in the community or in a hospital), and any underlying host abnormalities, such as immunodeficiency(**36).**

Due to their immature immune systems, neonates, particularly those born prematurely, are more likely to suffer from lung infections during the neonatal period. This is one of the leading causes of infant mortality. Vitamin D is a steroid hormone that plays an important part in maintaining the proper levels of calcium and phosphorus in the bone, as well as in the bone's metabolic process and its development. Recent studies have shed light on the role that vitamin D plays in the regulation of glucose homeostasis, as well as in cardiovascular disease, the immunological system, and cance (**37).**

In adults, a vitamin D deficiency is linked to an increased risk of developing numerous malignancies, diabetes mellitus (DM), rheumatoid arthritis, and multiple sclerosis. Insufficient vitamin D has been linked to type 1 diabetes, atopy, and allergies in children and infants. This association was found in both older children and younger children. In addition to this, it was found that children who had rickets as a result of a lack of vitamin D also had pneumonia. In point of fact, numerous studies have pointed to the significant part that vitamin D plays in the operation and control of the immune system. This is due to the fact that 1, 25-dihydroxy vitamin D can stimulate the innate immature response to a pathogen (**38).**

Because significantly lower concentrations of 25-hydroxyvitamin D were found in children with community-acquired pneumonia compared with healthy controls, young children with low levels of vitamin D are at risk for developing pneumonia. This is due to the fact that children with pneumonia had significantly lower concentrations of 25-hydroxyvitamin D than healthy controls (**39).**

Researchers looked at the levels of serum 25(OH)D in neonates with pneumonia and their mothers and found that both groups had a lower concentration than newborns and their mothers who were

healthy. (Mohamed and Al-Shehri, 2013) tested the cord blood of 206 newborns for 25 (OH) D and reviewed their medical records during the first two years of their lives. They found that a lower level of 25 (OH) D in cord blood was associated with a higher risk for acute lower respiratory tract infection (LRTI) in early life. This was discovered after the researchers noticed that the medical records of the newborns were reviewed during the first two years of their lives**(40).**

Because vitamin D can modulate the expression of specific tolerogenic genes during pregnancy, which are related to diseases other than congenital rickets, a lack of vitamin D in pregnant women has been reported to increase the risk of respiratory tract infection in their offspring. This is due to the fact that vitamin D deficiency in pregnant women causes their offspring to have a higher risk of respiratory tract infection. The current hypothesis is that having low levels of vitamin D is a risk factor for newborn pneumonia, and its bad prognosis can also be validated by the meta-analysis, which indicated that vitamin D treatment could decrease the number of events connected to respiratory tract infections (**41).**

In addition, the comprehensive analysis found that taking vitamin D supplements during pregnancy may reduce the risk of respiratory tract infections in kids. A more recent systematic review and meta-analysis demonstrated a strong association between levels of vitamin D and both the occurrence and severity of lower respiratory tract infections (LRTI). Although McNally et al., 2009 did not find a significant difference in the levels of vitamin D between the children who had LRTI and the controls, they did find that vitamin D deficiency was strongly related with admission to the paediatric ICU(**36).**

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