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Vitamin D3 action in the immune system of the newborn and zinc as immunomodulator

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Abstract

In recent years there has been an increase in the survival of critically ill newborns thanks to advances in the area of Neonatology, bringing with it the development of multiple pathologies, with the consequent increase in the risk of presenting perinatal infections, especially in the group corresponding to prematurity, the incidence and severity of infections in the newborn being well documented, which is largely due to immaturity in both the cellular and humoral response. Reporting a limited functional capacity of all components, in addition to observing quantitative and qualitative deficiencies of the cellular components of the immune system, so it is important to develop safe strategies such as supplementation with nutrients, which allow improving the immune response in the body, of these children.

Two decades ago, it was documented that Vitamin D3 in addition to having a regulatory function in the homeostasis of calcium and phosphorus has a relevant role in the modulation of the immune response, Its action is exerted through the union with its nuclear receptor and intervenes activating transcription factors The Receptor is present in cells of different tissues and of the immune system, such as dendritic cells, macrophages and T lymphocytes. It is known that: the immune system can be divided into two defense mechanisms or responses: the innate response and the acquired one. The innate response is made up of cellular and humoral components and does not improve after exposure to a specific antigen. About the Zinc (Zn) like trace element it can to participate in the modulation of the inflammatory response, it has linked very closely to the immune system, favoring the Th1 citokines production, development B lynphocytes and it can to influnece the antibodies production, especially IgG. Then in this time we go to review the recomendation in the literature, and how this elements can positively influence the immune response.

Conclusion: Within the comprehensive management that must be taken in the critically ill newborn, especially in the premature patient, we must consider micronutrients and their ability to influence the immune response, which is why the use of immunomodulators such as vitamin D (400 international units) is important. per day as a prophylactic and up to 1000 international units per day in deficiency) and with respect to Zinc, at appropriate doses Preterm: 300 micrograms of elemental zinc per kilo per day added to parenteral nutrition, and in newborns of term 100 mcgkg and the same in nutrition pareneral, further research on these micronutrients is required.

Introduction: As is known to all, the immune system can be divided into two defense or response mechanisms: the innate response and the adaptive or acquired response. The innate response probably present in all multicellular organisms, made up of cellular and humoral components. It acts against any harmful agent, but is nonspecific, recognizes a limited number of agents (approximately 103) has a limited number of receptors encoded by germ cells and that are present on the surface.It includes the skin and external defense mechanisms, mucous membranes, ciliated epithelia, cellular elements (eosinophils, basophils, neutrophils, platelets and monocytes, in addition to mast cells, epithelial, endothelial, dendritic, natural killer (NK) complement defensins, cytokines, coagulation factors and acute phase proteins such as C-reactive protein and fibronectin.

Adaptive immunity: capable of recognizing a wide range of foreign substances (approximately 108), related or not to microbial agents, through receptors that are generated particularly in lymphocytes and that are the product of complex genetic rearrangements. Thus, while natural immunity distinguishes only different classes of microbes, the adaptive one distinguishes different microbes of the same class or even different antigens of the same microbe. The acquired immune response is made up of cellular elements that respond differently to foreign antigens to which they have been previously exposed; includes T lymphocytes, B lymphocytes, and focal lymphocytes. In general, it requires the integration of different functions for the proper antigen processing. The phagocytic cells involved process the antigens and present them to the primary effector cells, the mature T lymphocytes. They recognize the presented antigens through specific surface receptors, become activated and proliferate rapidly with an increase in the number of T cells. T cells function in a variety of pathways either as cytotoxic or secondarily as producers of cellular messages that act on other cells, such as B lymphocytes, which mediate the elimination of pathogens through the production of antibodies.

Innate Immunity:
Phagocytes:
Production of granulocytes: The development of mature neutrophils capable of chemotaxis, phagocytosis, and

destruction of microorganisms is a vital aspect in the maturation of the defense immune system.Total granulocytes can be divided into two compartments:
a) Depot neutrophils: product of the sum of all postmitotic neutrophils (metamyelocytes, bands and segmented) whose number in adults is 4-7 x 109 cells / kg. While in newborns it only has 25% of them
b) The proliferative neutrophil compartment is integrated as the progenitors of neutrophils capable of dividing (myeloblasts, promyelocytes, myelocytes), adults have 1-2 x 109 cells / kg, while in newborns only ¼ part is found from them. Granulocyte and macrophage precursors (CFU-GM) can be found at 6-8 weeks in the yolk sac and at 8-12 weeks in the liver, and bone marrow. When examining the bone marrow, at 11- 12 weeks 23% of the cells are granulocytes.

Granulocites or neutrophils: in preterm newborns they have functional defects in all aspects, since they present a decrease in the migration capacity and the number of surface adhesion glycoproteins. In the same way, they show great cellular rigidity, decreased microfilament contractility, and less microbicidal activity. There is also an alteration in phagocytosis, O2 metabolism, and hydroxyl radical production.

Monocytes and Macrophages: They are found initially at 4 weeks in the vital sac and until the second trimester in the bone marrow. Its production in the liver and fetal bone marrow is similar to that of adults, but its function is diminished. Decreased production capacity of cytokines such as IL-6, decreased migration capacity, and chemotaxis have been documented.

Natural Killer NK Cells: Non-phagocytic cells responsible for cell-mediated cytotoxicity. Its ability to smooth pathogens is increased by IL-2, IFN α, β, γ present in the fetus between 8-13 weeks of gestation. Its function is between 15-65% of activity with respect to that of the adult. In neonates only 50% -80% antibody-dependent cytotoxicity is expressed compared to adults.

Complement: An integral part of the innate immune system made up of multiple proteins, they can be activated by the classical or alternate pathway that converge at the end, their terminal C5-9 portion is bactericidal specific for Gram negative organisms. Gram positive bacteria are resistant to lysis by complement. It is not transferred to the product through the placenta. SE produced by fetal tissue before week 18, SE found C2 and C4 in fetal liver at week 8, C3 and C5 at week 12 and C1 in fetal intestine at week 19. It is found in small quantities during the first trimester of pregnancy, in the term NB, the complement levels are 50% of those documented in the adult, but gradually increase until reaching normal levels between 6 and 8 months of life.

Cytokins: Pro-Inflammatory
They are soluble factors that modulate cell proliferation, differentiation and secretion activity, they are known as cytokines, interleukins, interferons and hematopoietic growth factors. In recent years, nutrition and its way of influencing health and disease, genetics and at the molecular level have taken on great importance, since its usefulness has become clearer. Diet-genome interactions can affect health and disease in several interconnected pathways including RNA expression, (transcriptome), epigenetic modifications (epigenome), intermediate metabolites (metabolome including lipidome and proteome) as well as microbiological communities that reside in the gastrointestinal tract (Microbiome).Some may include pathways of interconnectivity called inflammasomes, which speak to the responses of functional and sensory receptors that regulate the activation of the innate immune system in response to infections and molecules derived from host proteins.

Nutrigenetics:As non-genetically identical human beings and living in different environments, each individual's response to the type of diet they eat will always be different. Nutrigenetics refers to the interactions between nutrients and the gene (gene-nutrient) and how an individual responds to a certain diet based on their genome.Therefore, it is considered that an intervention in the diet can prevent the results of some diseases, this is complex and not only requires knowledge of how a singular nutrient can affect an immune system, but also how the mixture of nutrients interact to modulate functions biological.

Nutrigenomics: It refers to the study of the effects of how diet (food and food constituents) can alter individual genetic expression and encompass nutritional factors that protect the genome from damage. In other words, interactions between diet and the genome can affect health and disease through many interconnected ways (transcriptome, epigenome, metabolome, lipidome, etc.).Once we have already talked about the newborn's immune system both in innate and acquired immunity, and knowing the topics of Nutrigenomic, Nutrigenetic, we can talk about how micronutrients can intervene favorably in this inflammatory response of the newborn.

Vitamin D: Classically the hormonal actions of vitamin D related to mineral metabolism and skeletal health are widely known. The discovery of receptors for vitamin D in most cells and tissues has indicated that it has other roles in health than just that tissue. Actions include, among others, the regulation of cell proliferation, apoptosis, and angiogenesis. Studies have shown that in both the preterm and the term newborn, the storage of vitamin D at birth depends on the maternal 25-Hydroxyvitamin D because the fetus obtains it from its mother. At birth, regardless of gestational age, neonatal 25-

hydroxyvitamin D levels are 50-70% derived from the mother. In children born prematurely, vitamin D deficiency can lead to rickets, also known as osteopenia of prematurity or metabolic bone disease of prematurity.

Incidence: it can be increased above 55% in newborns weighing <1000 g) in which there is also an increased risk of presenting respiratory tract infections, or development of bronchopulmonary dysplasia, as well as growth disorder, and seizures.Guidelines have previously been published by the American Academy of Pediatrics that recommend supplementing with 200-400 IU / day in preterms fed only enteral. While in Europe according to the guidelines of ESPGHAN (European Society of Gastroenterology, Hepatology and Pediatric Nutrition) the supplement is indicated between 800-1000 IU / day) . Separate guidelines have recently been published in Central Europe, suggesting that enteral fed preterm infants should be supplemented with vitamin D at a dose of 40-800 Units per day within the first days of life and continue until 40 weeks of corrected gestational age, Vitamin D deficiency has also been associated with the development of cardiovascular diseases, various types of cancer, and autoimmune disorders such as type 1 diabetes Mellitus, (T1D) multiple sclerosis, and inflammatory bowel disease.

Regarding the immune response, vitamin D is one of the most pleiotropic molecules. It plays an important role in calcium metabolism, it also does it in lung health and the immune system, epidemiological studies have linked the insufficiency of this vitamin with asthma and allergic diseases, such as atopic dermatitis.The synthesis of vitamin -d3, occurs in the skin, in this it is converted into previtamin D3 in response to exposure to ultraviolet light (wavelength 290-315). Vitamin D3 obtained from pre-vitamin in the skin or by intestinal absorption of dietary components, binds to vitamin D-binding protein (DBP) in circulation). DBP is a highly polymorphic multifunctional protein and is produced in large quantities in the liver, it is responsible for transporting vitamin D to the same organ. Here, vitamin D3 is hydrolyzed by the enzyme 25-hydroxylase (CYP2R1) turning into 25 (OH) D3, being the main circulating form of vitamin D in the body.

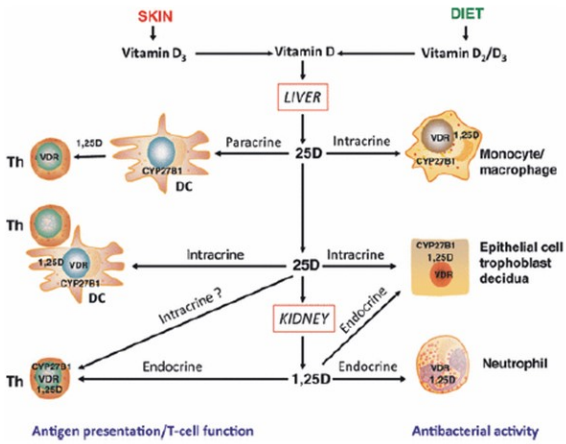
In the last decade, the perspective on how this vitamin influences human health has changed dramatically based on the findings that the Vitamin D receptor (VDR) and the vitamin D activating enzyme 1-α-hydroxylase (CYP27B1) are expressed in many types of cells which are not involved with mineral and bone metabolism, which has an important impact on many aspects that were not known. Especially immunologically. Its extrarenal synthesis of the active metabolite calcitriol (1,25 (OH) 2D- by immune cells and peripheral tissues has been proposed as an immunomodulatory property similar to the local activation of cytokines.

Vitamin D And Innate Immunity: It is an important stimulator of this immune response: it increases the antimicrobial effects of macrophages and monocytes, which strengthens against pathogens such as Mycobacterium tuberculosis. In addition, it increases chemotaxis and phagocytic capacities in innate immune cells, the complex of calcitriol, VDR and retinoid X receptor directly activates the transcription of antimicrobial peptides such as the β2 defensins 8DEFB) and the antimicrobial cathelicidin peptide (hCAp18).It acts as a signal for other cytokines such as interferon-γ or IL-4, as well as an effect on the expression of CYP27V1. Human cathelicidin (Hcap18) causes destabilization of microbial membranes, is highly regulated in response to infections and acts against bacteria, viruses and fungi. In severe infections, the percentage of innate granulocytic cells such as neutrophils is very high. Significantly lower serum levels of 25 (OH) D have been found in critically ill sepsis patients, which could be associated with a decrease in the concentration cathelicidin antimicrobial protein , and could support the theory that vitamin D regulates antimicrobial protein levels being crucial in infection control.

Low concentrations of calcitriol have been linked to an increase in mortality caused by severe infections in patients with end-stage renal disease and low levels have been associated with an increase in the frequency of respiratory infections, including influenza, chronic obstructive pulmonary disease, and allergic asthma, Randomized controlled study with the use of fortifiers in human milk in 247 vitamin D patients in Mongolia, (baseline 25 (OH) D) level of 7 ng / mL showed a significant reduction in respiratory tract infections at 3 months of age, (study period).In addition to fighting directly against microorganisms, monocytes and other antigen-presenting cells (APC) in particular dendritic cells (DC) are important targets for the immunomodulatory effects of vitamin D.These antigen-presenting cells are responsible for initiating the adaptive or acquired response, since they present antigens to T and B cells, and can modulate them by their immunogenic or tolerogenic signaling such as cytokines and the expression of co-stimulatory molecules. It has been shown that calcitrium and its analogues can alter the function and morphology of dendritic cells and induce a more tolerant immature state.

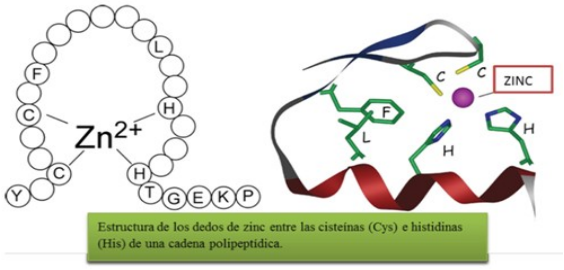
Vitamin D And Adaptive Immune Response:It has been shown that the nuclear VDR expression in T and B lymphocytes. In B lymphocytes, it has antiproliferative effects such as inhibition of differentiation, proliferation, initiation of apoptosis, and decreases immunoglobulin production, which was considered to be indirectly mediated by helper T lymphocytes. Direct effects of calcitriol on B cell homeostasis have been demonstrated, controlling the activation of B cells through apoptosis, which is clinically important in autoimmune diseases that produce autoreactive b cells. At the level of T cells, vitamin D has an important immunomodulatory effect in its different forms.

Influencing by various mechanisms:
1.- Direct on the endocrine effects of T cells mediated by systemic calcitriol pathway
2.- Direct in intracrine conversion of 25 (OH) D to calcitriol by T cells
3. Direct paracrine effect of calcitriol on T cells followed by conversion of 25 (OH) D to calcitriol by monocytes or dendritic cells
4. Indirect effects on the presentation of antigens to T cells through the localized pathway of APC affected by calcitriol.



Therefore, it is suggested that vitamin D not only supports innate immunity but also adaptive immunity and supplements with vitamin D.

Zinc as an Immunomodulator:



structure of the zinc fingers between the cysteines (Cys) and histidines of a polypeptide chain

Zinc is well known as an essential cofactor for the organism, a micronutrient with a very important role in reproduction, growth, development and cellular metabolism. Approximately 300 enzymes are known to require Zn for their metabolic activity called metalloenzymes. An enzyme is considered a metalloenzyme when the removal of Zn causes a reduction in activity without affecting the enzyme activity. The growth response observed in children who are given Zn supplements is an example of the relationship to the role that this metal has as a modulator in protein synthesis, in principle due to an increase in the activity of Zn. RNA polymerase. Zn is also important in the synthesis of proteins, nucleic acids, in cell division, in the function and stability of the cell membrane. Nucleoproteins contain it in large quantities and are probably involved in the genetic expression of various proteins - regulatory function. The mediating cells in the immune response decrease in Zn deficiencies, which is why it is proposed that it has a regulatory role in the immune response and can then act as a modulator in the susceptibility to infections.In this sense, its importance for the development and normal function of neutrophils and "natural killer" (NK) cells has been demonstrated. It also influences certain functions of T lymphocytes, such as activation, the production of Th1 cytokines, the development of B lymphocytes and the production of antibodies, especially IgG. It also has to do with the activity of macrophages, is a regulator of lymphocyte apoptosis and modulates the oxidative stress that is generated during the inflammatory response. Regulates the genetic expression of inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin 1b (IL-1b), known generators of reactive oxygen species (ROS), and this may be an additional mechanism by which this element can be functioning as a regulator of the cellular redox state in the human organism.

It is currently known that under conditions of Zn deficiency, the production of interleukin 2 (IL-2) decreases as a companion of T lymphocytes, also observing a decrease in their subpopulations, a situation that can improve when supplying the mineral. This micronutrient is considered non-toxic to humans in prescribed doses of less than 30 mg of Zn per day in children. Furthermore, at these doses, it does not show carcinogenic, mutagenic or teratogenic activity. Antioxidant Properties of Zinc: Zn deficiency has been associated with high levels of oxidative damage in tissues including oxidation to lipids, proteins, and DNA. The effects of this metal as an antioxidant were proposed in the late 1980s and comprise 2 different mechanisms:
1. The protection of the sulfhydryl groups of proteins and enzymes against the attack of ROS (example: alanyl tRNA synthetase, class 1 tRNA synthetase, farnesyltransferase, DNA proteins linked to Zn, among others).

2. Reduction of the formation of the hydroxyl radical (OH˙) from hydrogen peroxide (H2O2) through the prevention of ROS formation, or as an antagonist of transition metals such as iron (Fe) and copper (Cu).

Conclusion: In recent decades, research into vitamin D has confirmed important interactions between vitamin D and cells of the innate and adaptive immune system. Data have shown that a broad spectrum of tissue cells, including immune cells,

express enzymes that metabolize vitamin D, providing a biologically plausible mechanism for the local, auto, and paracrine conversion of native circulating forms to the active form calcitriol. . This process appears to be essential for normal immune function, and therefore impaired or insufficient vitamin D levels can lead to dysregulation of immune responses.

Within the comprehensive management that must be taken in the critically ill newborn, especially in the premature patient, we must consider micronutrients and their ability to influence the immune response, which is why the use of immunomodulators such as vitamin D (400 international units) is important. per day as a prophylactic and up to 1000 international units per day in deficiency) and with respect to Zinc, at appropriate doses Preterm: 300 micrograms of elemental zinc per kilo per day added to parenteral nutrition, and in newborns of term 100 mcgkg and the same in nutrition pareneral, further research on these micronutrients is required. As of yet, there is no global consensus on the recommended target serum level and optimal mode of vitamin D supplementation and Zinc, further clinical trials are needed to determine it.

Biography:

Dr. Maria Bertha Romo Almanza, completed her postgraduate degree in Neonatology at the National Institute of Perinatology, in Mexico City, completing this specialty at 30 years edge (2009), previously she has a specialty in Pediatrics at the Children's Hospital in Saltillo Coahuila, currently she is Chief in charge in Neonatology Inensive Care Unit at the Guadalupe Victoria Maternity and Child Hospital of Atizapan de Zaragoza since 5 years ago . Previously she was Chief in charge in NICU at Star Médica Luna Parc Cuautitlan Izcalli, where she continues his private practice. Instructor Neonatal CPR, member from ANEM , APROLAM She has published articles in international Journals .

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