Vitamin D for Covid-19?

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A small survey of literature about Vitamin D and inhibition and expression of interleukins and tumor necrosis factors. Could Vitamin D have a possible role in Covid-19 Cytokine Release Syndrome? A study of its role when tocilizumab is used exists, and therefore Vitamin D could be considered when tocilizumab is involved in the mitigation of the cytokine storm. However, another question also exists and it is the following. Might Vitamin D induce antimicrobial peptides to reduce SARS-CoV-2 replication?

Keywords: Cytokines, Interleukins, TNF, Vitamin D, Tocilizumab, Drugs.

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In [1], we have considered some literature about Covid-19 Cytokine Release Syndrome, known as "cytokine storm". Cytokines are proteins which are released by many different cells in the body, including those of the immune system. Then, these proteins have a role in coordinating the body's response against infection and trigger inflammation. When it happens that excessive or uncontrolled levels of cytokines are released, with a consequent activation of more immune cells, the body suffers a hyper-inflammation, that is, a "cytokine storm". The cytokine storms are a common complication of Covid-19, influenza, SARS and MERS. "The term was popularized largely in the context of avian H5N1 influenza virus infection, bringing the term into popular media" [2].

In [1] we mentioned two articles, [3] and [4], where Vitamin D is considered.

Let us start from [4], where M. Silberstein asks: "*Vitamin D: A simpler alternative to tocilizumab for trial in COVID-19?*". Then, a possible question is: could Vitamin D have a possible role in Covid-19 Cytokine Release Syndrome? The question is posed in this form, because tocilizumab is a drug used against Covid-19 Cytokine Release Syndrome.

"Tocilizumab, also known as atlizumab, is an immunosuppressive drug, mainly for the treatment of rheumatoid arthritis ... . It is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R). Interleukin 6 (IL-6) is a cytokine that plays an important role in immune response and is implicated in the pathogenesis of many diseases, such as autoimmune diseases, multiple myeloma and prostate cancer". https://en.wikipedia.org/wiki/Tocilizumab

Then, let us search for literature, at the beginning, about Vitamin D and interleukins.

Actually, in [5], we find Vitamin D involved with tocilizumab. The article is entitled "*1,25-dihydroxy Vitamin D3 and Interleukin-6 Blockade Synergistically Regulate Rheumatoid Arthritis by Suppressing Interleukin-17 Production and Osteoclastogenesis*". It is told that "Immune cells express the vitamin (vit) D receptor, and vit D is a potent immune-modulator. A negative correlation between serum vit D levels and rheumatoid arthritis (RA) disease activity has been reported. Therefore," the authors of [5] "aimed to investigate if the sufficient serum vit D level is helpful to control disease activity in RA patients treated with interleukin (IL)-6 receptor antibody tocilizumab". RA patients taking tocilizumab were enrolled, and data were collected retrospectively. "RA patients treated with IL-6 antibody show a better response when they have sufficient serum vit D. Tocilizumab and $1,25(OH)_2D$ synergistically suppress IL-17 production and osteoclast differentiation in RA patients".

In [6], "*Vitamin D as a Principal Factor in Mediating Rheumatoid Arthritis-Derived Immune Response*" is discussed in a mini-review. The abstract tells "Rheumatoid arthritis (RA) is a systemic

multifactorial autoimmune disorder. ... Serum levels of vitamin D (VD) are involved in the regulation of various immune responses. Vitamin D is a key signaling molecule in the human body that maintains calcium as well as phosphate homeostasis. It also regulates the functions of the immune system and, thus, can play a substantial role in the etiology of various autoimmune disorders, including RA. Low serum VD levels have been found to be associated with a higher risk of RA, although this finding has not been replicated consistently. The molecular mechanisms by which VD influences autoimmunity need to be further explored to understand how variation in plasma VD levels could affect the pathogenesis of RA. This mini-review focuses on the influence of VD and its serum levels on RA susceptibility, RA-associated complexities, treatment, and transcriptome products of key proinflammatory cytokines, along with other cytokines that are key regulators of inflammation in rheumatoid joints".

In [6] it is told that the cytokines involved in RA can be grouped into two main categories of proinflammatory and anti-inflammatory cytokines. "Tumor necrosis factor alpha (TNFα), interleukin1 (IL-1), interleukin6 (IL-6), and interleukin17 (IL-17) are key proinflammatory cytokines. ... IL-6 also regulates the activation and differentiation of various immune cells. ...Since the focus of this short review is on the effect of VD on proinflammatory cytokines, anti-inflammatory cytokines are not discussed" in [6].

The section 5 of this reference discusses Vitamin D and Tumor Necrosis Factor-Alpha (TNFα). Among the papers mentioned we find [7]; it is a study "conducted on healthy women" that "showed an inverse correlation between VD and TNFα concentration and suggested the preventive role of VD against inflammatory conditions". Abstract of [7] tells that "Circulating 25 hydroxyvitamin D (25 (OH)D), an accurate measure of vitamin D status, is markedly greater in individuals with increased exposure to ultraviolet B (UVB) light via sunlight or the use of artificial UV light. Aside from the known relationship between vitamin D and bone, vitamin D has also been implicated in immune function and inflammation. Furthermore, a mass of evidence is accumulating that vitamin D deficiency could lead to immune malfunction. Our overall objective was to study the relationship between vitamin D status (as determined by serum 25(OH) D concentrations) and inflammatory markers in healthy women".

Sections 6-9 of Ref.[6] are discussing Vitamin D and interleukins and other cytokines. In the Section 7, it is considered Interleukin-6. "Serum levels of VD have been reported to be inversely related to serum IL-6 levels" [8]. Ref.8 tells that "Vitamin D deficiency has been linked to various inflammatory diseases. However, the mechanism by which vitamin D reduces inflammation remains poorly understood". In [8], the researchers "investigated the inhibitory effects of physiologic levels of vitamin D on LPS-stimulated [lipopolysaccharide] inflammatory response in human blood monocytes and explored potential mechanisms of vitamin D action". Two forms of the vitamin D, 1,25(OH)2D3, and 25(OH)D3, have been considered". "In conclusion," - tell the authors, - their "study identified the upregulation of MKP-1 by vitamin D as a novel pathway by which vitamin D inhibits LPS-induced p38 activation and cytokine production in monocytes/macrophages".

In [9], the reference is entitled "*Inhibition of p38 by vitamin D reduces interleukin-6 production in normal prostate cells via mitogen-activated protein kinase phosphatase 5: implications for prostate cancer prevention by vitamin D*". In the abstract: "Activation of p38 and downstream production of interleukin 6 (IL-6) are proinflammatory. Inflammation and IL-6 overexpression have been implicated in the initiation and progression of prostate cancer. 1,25D pretreatment inhibited both UV- and tumor necrosis factor alpha-stimulated IL-6 production in normal cells via p38 inhibition. Consistent with inhibition of p38, 1,25D decreased UV-stimulated IL-6 mRNA stabilization. The ability of 1,25D to up-regulate MKP5 was maintained in primary prostatic adenocarcinoma cells but was absent in metastases-derived prostate cancer cell lines. The inability of 1,25D to regulate MKP5 in the metastasis-derived cancer cells suggests there may be selective pressure to eliminate key tumor suppressor functions of vitamin D during cancer progression. These studies reveal MKP5 as a mediator of p38 inactivation and decreased IL-6 expression by 1,25D in primary prostatic

cultures of normal and adenocarcinoma cells, implicating decreased prostatic inflammation as a potential mechanism for prostate cancer prevention by 1,25D".

1,25D is 1,25-dihydroxyvitamin-D_3. "1,25-Dihydroxyvitamin D(3) (1,25D) is known primarily as a regulator of calcium, but 1,25D also promotes phosphate absorption from intestine, reabsorption from kidney, and bone mineral resorption" [10].

In [11], we find a work entitled "*Vitamin D Induces Interleukin-1β Expression: Paracrine Macrophage Epithelial Signaling Controls M. tuberculosis Infection*". "Although vitamin D deficiency is a common feature among patients presenting with active tuberculosis, the full scope of vitamin D action during Mycobacterium tuberculosis (Mtb) infection is poorly understood." The authors used the hormonal form of vitamin D, 1,25-dihydroxyvitamin D (1,25D). The researchers "focused on the role of 1,25D- and infection-induced interleukin 1β (IL-1β) expression in response to infection. 1,25D enhanced IL-1β expression via a direct transcriptional mechanism. Secretion of IL-1β from infected cells required the NLRP3/caspase-1 inflammasome. The impact of IL-1β production was investigated in a novel model ... [The] data provide evidence that the anti-microbial actions of vitamin D extend beyond the macrophage by modulating paracrine signaling, reinforcing its role in innate immune regulation in humans."

In [12], the research is entitled "*Relationships among interleukin-6, tumor necrosis factor-α, adipokines, vitamin D, and chronic periodontitis*". The aim of the researchers was that of exploring "relationships among serum adipokines, vitamin D, and clinical and microbial parameters of chronic periodontitis before and after treatment". "Weight, height, and smoking status were recorded for 56 patients with chronic periodontitis. Plaque, gingivitis, bleeding on probing, suppuration, probing depth, and clinical attachment level were measured at all teeth present. Subgingival biofilm samples from each tooth were analyzed for levels of 40 bacterial species using checkerboard DNA-DNA hybridization. Serum levels of interleukin-6 (IL-6), tumor necrosis factor-α, adiponectin, leptin, resistin, and vitamin D were measured at baseline. Sample collection was then performed in a subset of the population 6 months after therapy (n = 17). Serum samples were analyzed ...". About the results, the authors write: "There were positive correlations between adiponectin/vitamin D and between IL-6/leptin, negative correlations between IL-6/vitamin D and leptin/vitamin D, but no associations between serum analytes and clinical or microbial parameters. Sex and body mass index were associated with levels of adipokines. Periodontal therapy improved clinical and microbiologic parameters but did not influence the levels of serum analytes". The CONCLUSION is also interesting "Adipokines and IL-6 levels were affected by sex and body mass index".

In [13], we find discussed: "*Vitamin D derivatives: calcitriol and tacalcitol inhibits interleukin-6 and interleukin-8 expression in human nasal polyp fibroblast cultures*". "Biologically active vitamin D3 (VD) derivatives possess modulatory activities on immunological and inflammatory responses which can be reflected by altered levels of pro-inflammatory chemokines. Nasal polyposis (NP), defined as a chronic inflammatory process of upper respiratory system, could be influenced by VD derivatives. The purpose of this study was to investigate the influence of 1alpha,25-dihydroxyvitamin D3 (calcitriol) and 1alpha,24(R)-dihydroxyvitamin D3 (tacalcitol) on the secretion of IL-6 and IL-8 by fibroblasts derived from NP. ... Treatment with calcitriol or tacalcitol inhibits the synthesis of both IL-6 and IL-8 compared to the control group. The dose dependence of this effect has been confirmed. VD derivatives influence was marked at higher concentrations. Significant interleukin decrease was observed at 10(-5) and 10(-4) for calcitriol and 10-4 in the case of tacalcitol". The authors in [13] tell that their study "demonstrates that calcitriol and tacalcitol are capable of affecting pro-inflammatory cytokine (IL-6 and IL-8) levels in NP cultures. Our data imply a potential therapeutical application of topical VD derivates in NP and warrant further investigation".

"Calcitriol is the active form of vitamin D, normally made in the kidney". https://en.wikipedia.org/wiki/Calcitriol ; "Tacalcitol (1,24-dihydroxyvitamin D3) is a synthetic vitamin D3

analog. Tacalcitol is marketed under several names, including Curatoderm and Bonalfa". https://en.wikipedia.org/wiki/Tacalcitol

By means of the previous works, we have searched for an answer to the question "Could Vitamin D have a possible role in Covid-19 Cytokine Release Syndrome?". A study [5] of the role of this vitamin when tocilizumab is used exists, and therefore Vitamin D could be considered when tocilizumab is involved in the mitigation of the cytokine storm. And now, let us consider the other question "Might Vitamin D induce antimicrobial peptides to reduce SARS-CoV-2 replication?". The reason of it is in Ref.3, entitled "*Current status of potential therapeutic candidates for the COVID-19 crisis*".

In [3], it is told that "**Vitamin D might induce antimicrobial peptides to reduce SARS-CoV-2 replication**". However, no references are given where this sentence is written. But a section in [3] tells that "Vitamin D is known to modulate the innate and adaptive immune system, and its deficiency is associated with increased autoimmunity as well as in an increased susceptibility to infection (Aranow, 2011) [14]. Grant et al. (2020) [15] pointed the role of vitamin D in reducing the risk of respiratory tract infections by COVID-19. Actions of mechanism of vitamin D include the induction of antimicrobial peptides (i.e., cathelicidins and defensins) that can reduce viral replication rate and impeding pro-inflammatory cytokines. Several clinical trials of vitamin D in patients with COVID-19 (i.e., NCT04334005, NCT04344041) are underway".

In [14], "*Vitamin D and the Immune System*", abstract tells that "It is now clear that vitamin D has important roles in addition to its classic effects on calcium and bone homeostasis. As the vitamin D receptor is expressed on immune cells (B cells, T cells, and antigen-presenting cells), and these immunologic cells are all capable of synthesizing the active vitamin D metabolite, vitamin D has the capability of acting in an autocrine manner in a local immunologic milieu. Vitamin D can modulate the innate and adaptive immune responses. Deficiency in vitamin D is associated with increased autoimmunity and an increased susceptibility to infection. As immune cells in autoimmune diseases are responsive to the ameliorative effects of vitamin D, the beneficial effects of supplementing vitamin D-deficient individuals with autoimmune disease may extend beyond the effects on bone and calcium homeostasis".

In [15], "*Evidence that Vitamin D Supplementation Could Reduce Risk*" of respiratory tract infections is discussed, also concerning the "epidemiology of influenza and COVID-19, and how vitamin D supplementation might be a useful measure to reduce risk. Through several mechanisms, vitamin D can reduce risk of infections. Those mechanisms include inducing cathelicidins and defensins that can lower viral replication rates and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing concentrations of anti-inflammatory cytokines". The authors in [15] tells that "several observational studies and clinical trials reported that vitamin D supplementation reduced the risk of influenza, whereas others did not".And also that "Evidence supporting the role of vitamin D in reducing risk of COVID-19 includes that the outbreak occurred in winter, a time when 25-hydroxyvitamin D (25(OH)D) concentrations are lowest; that the number of cases in the Southern Hemisphere near the end of summer are low; ... ". Some recommendation of assume vitamin D3 are given. However "Randomized controlled trials and large population studies should be conducted to evaluate these recommendations".

About NCT04334005 and NCT04344041 we have the following links.

"*Vitamin D on Prevention and Treatment of COVID-19 (COVITD-19)*"

"Vitamin D is a hormone precursor produced by our own body with the help of sunlight which has an important role on adaptive immunity and cellular differentiation, maturation and proliferation of several immune cells. Reduced levels of vitamin D in calves were positioned as the main cause of

bovine coronavirus infection in the past. Therefore, it seems plausible that the use of vitamin D as a nutritional ergogenic aid could be a potential intervention to fight against COVID-19 infected patients which remain asymptomatic or which have non-severe and severe symptoms". The study NCT04334005 "aims to investigate whether the use of vitamin D as an immune modulator agent induces significant improvements of health status and outcomes in non-severe symptomatic patients infected with COVID-19 as well as preventing COVID-19 health deterioration". It is hypothesized "that vitamin D will significantly improve hard endpoints related to COVID-19 deleterious consequences compared with a usual care control group". https://clinicaltrials.gov/ct2/show/NCT04334005

"*COvid-19 and Vitamin D Supplementation: a Multicenter Randomized Controlled Trial of High Dose Versus Standard Dose Vitamin D3 in High-risk COVID-19 Patients (CoVitTrial)*"

"Preclinical research suggests that the SARS-Cov-2 virus enters cells via the angiotensin converting enzyme 2 (ACE2). Coronavirus viral replication downregulates ACE2, thereby dysregulating the renin-angiotensin system (RAS) and leading to a cytokine storm in the host, causing acute respiratory distress syndrome (ARDS). Research also shows that vitamin D plays a role in balancing RAS and in reducing lung damage. On the contrary, chronic hypovitaminosis D induces pulmonary fibrosis through activation of RAS. Similarly, hypovitaminosis D has been strongly associated in the literature with ARDS, as well as with a pejorative vital prognosis in resuscitation but also in geriatric units, and with various comorbidities associated to deaths during SARS-Cov-2 infections. Conversely, vitamin D supplementation has been reported to increase immunity and to reduce inflammatory responses and the risk of acute respiratory tract infections". It is also told that "Vitamin D supplementation is mentioned as a potentially interesting treatment for SARS-Cov-2 infection but on a scientific basis with a low level of evidence until now". https://clinicaltrials.gov/ct2/show/NCT04344041

In [16], we find a preprint entitled: "*Tripartite combination of potential pandemic mitigation agents: Vitamin D, Quercetin, and Estradiol manifest properties of candidate medicinal agents for mitigation of the severity of pandemic COVID-19 defined by genomics-guided tracing of SARS-CoV-2 targets in human cells.*" In the abstract, we find that "Genes required for SARS-CoV-2 entry into human cells, ACE2 and FURIN," can be "employed as baits to build genomics-guided molecular maps of up-stream regulatory elements, their expression and functions in human body, including pathophysiologically-relevant cell types. Repressors and activators of the ACE2 and FURIN genes were identified based on the analyses of gene silencing and overexpression experiments as well as relevant transgenic mouse models". Panels of repressors and activators were then employed "to identify existing drugs manifesting gene expression signatures of the potential coronavirus infection mitigation agents. Using this strategy, Vitamin D and Quercetin have been identified as putative COVID-19 mitigation agents".

Now, let us consider other two works about Vitamin D.

In [17]: "The present aim was to propose an hypothesis that there is a potential association between mean levels of vitamin D in various countries with cases and mortality caused by COVID-19. The mean levels of vitamin D for 20 European countries and morbidity and mortality caused by COVID-19 were acquired. ... Vitamin D levels are severely low in the aging population especially in Spain, Italy and Switzerland. This is also the most vulnerable group of the population in relation to COVID-19. It should be advisable to perform dedicated studies about vitamin D levels in COVID-19 patients with diferent degrees of disease severity".

In https://www.news-medical.net/news/20200429/Low-levels-of-vitamin-D-may-be-linked-to-severe-COVID-19.aspx we find an article entitled "Low levels of vitamin D may be linked to severe COVID-19", by Tomislav Meštrović, Apr 29 2020. "A new observational study from the United States indicates that vitamin D insufficiency may play a significant role in the progression of coronavirus disease (COVID-19). The research titled 'Vitamin D Insufficiency is Prevalent in Severe COVID-19' is available on the preprint server medRxiv".

Let us conclude with two links and two different expressions about Vitamin D. One of the link is https://www.unitonews.it/index.php/it/news_detail/la-carenza-di-vitamina-d-un-fattore-di-rischio-linfezione-da-coronavirus 26 mar 2020, "La carenza di vitamina D: un fattore di rischio per l'infezione da Coronavirus?" where we find that "I Proff. Giancarlo Isaia ed Enzo Medico dell'Università di Torino sul possibile ruolo preventivo e terapeutico della vitamina D nella gestione della pandemia da COVID-19".

The other link is related to [19], and it is https://www.cebm.net/covid-19/vitamin-d-a-rapid-review-of-the-evidence-for-treatment-or-prevention-in-covid-19/

The authors tell that they found "no clinical evidence on vitamin D in COVID-19. There was no evidence related to vitamin D deficiency predisposing to COVID-19, nor were there studies of supplementation for preventing or treating COVID-19. There is some evidence that daily vitamin D3 supplementation over weeks to months may prevent other acute respiratory infections, particularly in people with low or very low vitamin D status. This evidence has limitations, including heterogeneity in study populations, interventions, and definitions of respiratory infections that include upper and lower respiratory tract involvement."

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