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Inhibitory effects of Vitamin D on inflammation and IL-6 release. A further support for COVID-19 management?

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Abstract. The ongoing worldwide pandemic of Coronavirus disease 2019 (COVID-19), raised the urgency to address knowledge gaps and to establish evidence for improving management and control of this viral infection. Throughout a keen analysis of the World Health Organization (WHO) most updated data, a gender-specific difference in the occurrence of infection was determined, which seems to correlate with patient's vitamin D status. Therefore, our purpose is to provide insights into the nutritional importance of vitamin D for its immunomodulatory effect, in order to help counteracting the COVID-19 pandemic. Novel interesting findings suggest that vitamin D, by inducing progesterone-induced blocking factor (PIBF), might regulate the immune response and also modulate cytokine IL-6, which appears to be increased in COVID-19 infections. Therefore, in addition to the standard recommendations to prevent the infection, supplementation of vitamin D might be considered an approach to help counteracting this global epidemic.

Key Words:
COVID-19, Vitamin D, Vitamin D deficiency, Progesterone-induced blocking factor, PIBF, IL-6, Interleukin 6.

Introduction

Since February 2020, the spreading of confirmed cases of COVID-19 infection has increased woldwide. In Italy, more than 100,000 people have been infected with the virus, and more than 10,000 have died. According to the Italian public health institution, Istituto Superiore di Sanità (ISS), approximately 60% of confirmed Coronavirus cases and 70% of deaths in the country so far have occurred in men. The mortality rate of Italian males seems to be higher in every age group compared to women (Table I). This gender differences have raised our interest on complementary potential risk factors for contracting the infection. Years of research show that women generally have a stronger immune system and are better able to fend off infections than men[1]. However, the response to COVID-19 seems quite controversial across all continents. Up to date, mortality due to the virus is the highest in the elderly to aged population worldwide.

A recent review[2] suggests a possible association between vitamin D deficiency and vulnerability to infection. A retrospective observational epidemiological survey on vitamin D levels in Italian population revealed total vitamin D (25-hydroxyvitamin D) deficiency in two regions of Northern Italy (Emilia Romagna and Veneto). The rate of vitamin D deficiency was 36%, and was slightly but significantly higher in men than in women (40% *vs.* 35%; p=0.003). A significant variation in the rate of vitamin D deficiency was found also throughout different age ranges, with a significant increase in the elderly[3]. According to recent national data, the two aforementioned regions are strongly affected by COVID-19, with the highest number of death, after Lombardia. The correlation of vitamin D deficiency and the gender-specific higher incidence of mortality caused by COVID-19 may provide some insights into the COVID-19 epidemic. Furtheremore, according to the COVID-19 disease situation dashboard from WHO, the countries of the Northen Hemisphere have the highest rates of infections and deaths (Figure 1). In this time of the year, from November to February, vitamin D production *via*

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Table I. Distribution of cases diagnosticated by Italian regional reference laboratories (N = 73,780) and of reported deaths (N = 6,801) by age and sex range. Modified by COVID-19 epidemic National update March 26, 2020 - 4:00 pm. Istituto Superiore di Sanità (ISS), Rome, Italy.

Age	Men				Women			
	N. Cases	% Cases per gender	N. Deaths (%)	% Deaths per gender	N. Cases	% Cases per gender	N. Deaths (%)	% Deaths per gender
0-9	244	57.5	0 (0.0)	0.0	180	42.5	0 (0.0)	0.0
10-19	261	51.2	0 (0.0)	0.0	249	48.8	0 (0.0)	0.0
20-29	1203	44.3	0 (0.0)	0.0	1510	55.7	0 (0.0)	0.0
30-39	2465	49.7	14 (0.6)	**82.4**	2494	50.3	3 (0.1)	**17.6**
40-49	4597	50.1	49 (1.1)	**73.1**	4570	49.9	18 (0.4)	**26.9**
50-59	7998	55.8	190 (2.4)	**78.5**	6337	44.2	52 (0.8)	**21.5**
60-69	8755	66.6	606 (6.9)	**79.7**	4394	33.4	154 (3.5)	**20.3**
70-79	9309	66.1	1846 (19.8)	**76.9**	4781	33.9	555 (11.6)	**23.1**
80-89	6195	56.7	1808 (29.2)	**66.9**	4734	43.3	894 (18.9)	**33.1**
≥90	887	35.1	273 (30.8)	45.0	1640	64.9	334 (20.4)	55.0
Unknown	135	56.0	0 (0.0)	0.0	106	44.0	0 (0.0)	0.0
Total	42049	57.6	4786 (11.4)	**70.4**	30995	42.4	2010 (6.5)	**29.6**

sunlight exposure is very small, due to lower ultraviolet (UV) radiation and shorter daytime. An interesting paper on the global epidemiology of vitamin D status previously showed that Asian people have a prevalence of vitamin D insufficiency in all age groups, whereas South American and African population have sufficient serum levels of vitamin D, possibly due to a longer exposure to sunlight and UV radiation throughout the year[4]. In the Middle Eastern countries, such as Iran or

Figure 1. COVID-19 disease situation dashboard. The Northern Hemisphere represents a higher rate of COVID-19 infections. Adapted from Coronavirus disease (COVID-19) Situation Dashboard from WHO (updated 31st March 2020).

Pakistan, clothing may play a crucial role in the high prevalence of hypovitaminosis D, despite the high UV exposure. Indeed, cultural, national, and dietary habits should be considered[5]. This correlation between vitamin D deficiency across the world and the countries most affected by the virus allows to assume that vitamin D may affect the course of COVID-19 infections.

Vitamin D

Vitamin D or calciferol, a fat-soluble vitamin[6] is chemically classified as a steroid[7]. Indeed, it can be considered a nutrient but it is also a secosteroid hormone, more recently proposed as a progesterone-like hormone[8]. There are two main sources of vitamin D: the dietary intake and the endogenous synthesis. The main food source is fish (such as salmon, mackerel, tuna, sardine) and cod liver oil, but traces can be found also in mushrooms. Vitamin D-fortified foods or dietary supplements might be an optimal source of extra vitamin D. The U.S. National Academy of Medicine considers 600-800 IU of vitamin D daily intake to be sufficient for the majority of the population, however the U.S. Endocrine Society recommends 1,500-2,000 IU per day[9,10]. Also, the European food safety authority (EFSA) defines 600 IU per day as an adequate intake, also for pregnant and lactating women. A maximum allowed threshold of 2,000 IU per day for healthy individuals was set by EFSA.

Endogenous vitamin D can be synthesized in the skin upon direct irradiation with UVB. Hypovitaminosis D during the winter season can be mainly attributed to lifestyle and environmental factors that reduce exposure to sunlight. Moreover, another risk factor for hypovitaminosis D is obesity, as vitamin D deficiency is strongly associated with metabolic syndrome in morbidly obese patients[11,12]. Emerging evidence[13] supports the beneficial role of vitamin D against autoimmune diseases, influenza, type-2 diabetes, heart disease, fractures, cancer and depression.

Immunomodulatory Activity of Vitamin D

Vitamin D is an immunomodulator molecule, attenuating strong pro-inflammatory reactions[14,15] and it downregulates the immune responses mediated by Th1 cells, by inhibiting the production of pro-inflammatory cytokines like IFN-γ, IL-6, IL-2, and TNF-α[16,17] (Figure 2). As recent preliminary data[18] showed that IL-6 significantly increases in the group of COVID-19 patients, the use of an adequate source of vitamin D might

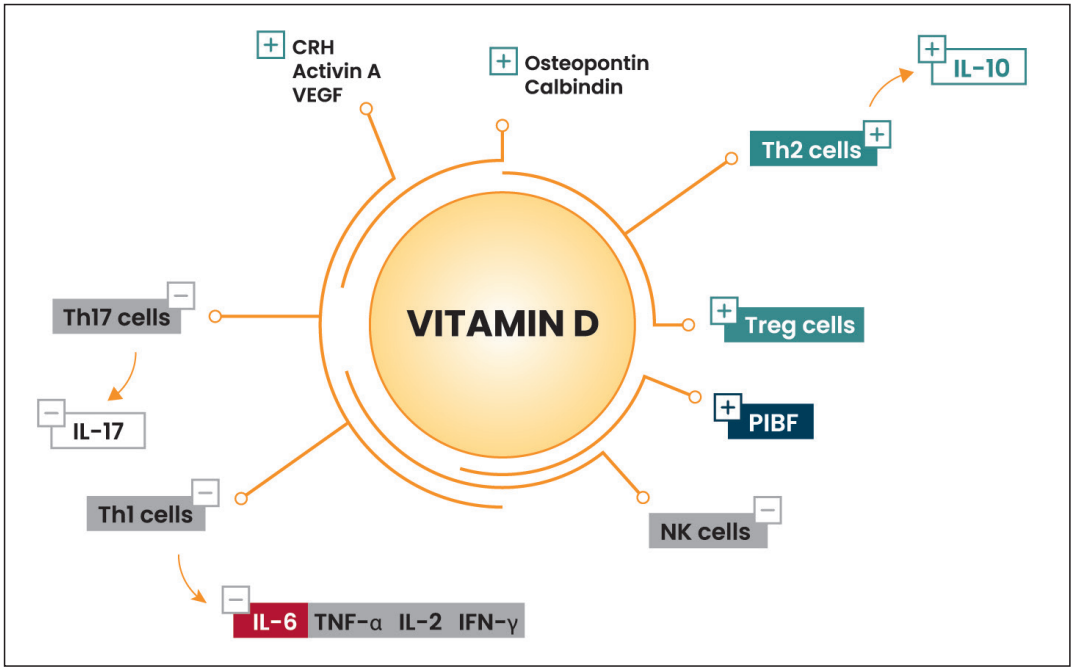

Figure 2. Vitamin D stimulates the release of corticotropin-releasing factor (CRF), activin A, vascular endothelial growth factor (VEGF), osteopontin, calbindin, progesterone-induced blocking factor (PIBF) and induces anti-inflammatory pathways (Th2 and Treg cells). Vitamin D inhibits the proinflammatory pathways (NK, Th1 and Th17 cells) and inhibits the production of pro-inflammatory cytokines like IL-6, TNF-α, IL-2, and IFN-γ.

help in reducing this pro-inflammatory response. This hypothesis can be better validated by recent investigations on vitamin D treatment in different pathological conditions featuring low serum 25(OH)D3 levels (diabetes, sickle cell anemia, multiple sclerosis, obesity, human immunodeficiency virus infection and tuberculosis). An experimental study reported significantly increased IL-6 mRNA expression in liver tissue of chronic hyperglycemia mice and the beneficial effects of vitamin D administration in down-regulating IL-6 expression and counteracting hypovitaminosis D[19]. In a clinical trial, reduction of the mRNA expression levels of IL-6 was also observed after 8 weeks administration of vitamin D in multiple sclerosis patients[20]. Furthermore, a three-month daily supplementation of vitamin D in children with sickle cell anaemia reduced the inflammatory milieu, including IL-6 levels[21]. On the other hand, the reduction of serum IL-6 levels was seen after a year-long daily intake of vitamin D in insulin resistent, overweight and obese subjects[22]. Moreover, the correlation of vitamin D deficiency in immunocompromised patients has been extensively examined, finding an increased risk of HIV progression and death. Indeed, significantly increased levels of IL-6 were reported in chronic HIV patients with vitamin D deficiency, (23%; $p<0.01$)[23]. Likewise, vitamin D deficiency is common in patients with tuberculosis and, the negative correlation between IL-6 levels and vitamin D increases as the disease progresses[24]. Cytokine IL-6 plays a major role in the pathogenesis and the clinical manifestations of tuberculosis, and it can be considered a valuable biomarker for this disease. A number of clinical trials demonstrated the adjuvant role of dietary vitamin D in preventing the oxidative stress and tissue damage in tuberculosis while modulating the IL-6 levels[24]. Moreover, a significant inverse correlation between serum vitamin D and IL-6 levels was reported in schizophrenia, renal cell carcinoma and Takayasu's Arteritis individuals[25-27]. Supplementation with 2,000 IU/day vitamin D for 12 weeks in patients with ulcerative colitis showed to prevent from systematic inflammation and decrease disease activity[28]. Another relevant study[29] showed a reduction of IL-6 secretion by trophoblasts from patients with gestational diabetes mellitus after treatment with vitamin D (2000 nM), supporting its anti-inflammatory activity at the feto-maternal interface. Such immunomodulatory activity of vitamin D might be extremely useful during pregnancy. Pregnant women undergo physiological adaptive changes that weaken their immune system during this period of time, therefore, they might be more susceptible to COVID-19 infection than the general population. The number of COVID-19 positive pregnant women is increasing and limited information is available about the clinical implications and the potential risk of vertical transmission. However, a small retrospective study, on pregnant women with COVID-19 reported no complicances for the new born correlated to infection of the foetus[30,31]. Pro-inflammatory cytokines proved to be associated with recurrent spontaneous miscarriage and preterm delivery. A significantly lower serum concentrations of the T-helper 2-type cytokines IL-6, IL-10 and IL-13 in women with missed abortions was found, but not in those with threatened abortions, compared to normal pregnant and non-pregnant women[32,33]. Progesterone is crucial for both the establishment and maintenance of pregnancy. During pregnancy, progesterone induces the expression of a protein called progesterone-induced blocking factor (PIBF), which mediates some of its immunological effects[34,35]. This family of proteins prevents the abortive effect of natural killer (NK) cells and blocks their activity, interfering with the arachidonic acid metabolism and inducing a Th2-biased immune response[36-38]. PIBF production is a characteristic feature of physiologic pregnancy and the determination of PIBF concentration in urine or in the serum of pregnant women might be useful to diagnose threatened premature pregnancy termination[39]. Recently, we found that, vitamin D is able to induce PIBF production in activated human peripheral lymphocytes similarly to progesterone. Considering the functional overlap in the immunological effects of progesterone and vitamin D, they might cooperate through PIBF induction in regulating the immune response. The immunomodulatory effect of vitamin D in lymphocytes may derive from common regulatory activities between progesterone and vitamin D. Indeed, our preliminary results showed that vitamin D acts more efficiently in progesterone-primed lymphocytes, significantly increasing PIBF levels, when administered along with progesterone[40]. This can be explained because progesterone increases the expression of vitamin D receptors (VDR) in peripheral lymphocytes in a concentration-dependent manner. These singular results suggest that vitamin D, by inducing PIBF, might cooperate with progesterone in regulating the immune response.

Vitamin D and the Respiratory Tract Infection

The expression of VDR in the lungs, suggests a possible influence of vitamin D in respiratory functions. Indeed, it was recently reported that, vitamin D reduces the risk and the incidence of respiratory infections, via its immunomodulatory effect[41]. Indeed, alterations of a single-nucleotide polymorphism in one of the gene encoding the VDR was correlated to an increased risk of acute lower respiratory tract infection during early childhood[42]. Furthermore, a recent meta-analysis[43] found that administration of vitamin D significantly reduces the risk of acute respiratory infections primarily in individuals with low vitamin D levels (<25 nmol/L). Another systematic review and meta-analysis, corroborated these data, showing that vitamin D supplementation decreases the events related to respiratory tract infections when compared to placebo. This relationship between vitamin D and respiratory infections and lung function, led to propose vitamin D as a protective 'seasonal stimulus' against influenza[44]. Therefore, there is consistent amount of data reporting a role for vitamin D in preventing respiratory tract infections, reinforcing its potential contribution in mitigating the present pandemic. Nonetheless, there is the need of more well-conducted clinical trials to reach definitive conclusions.

Conclusions

This paper highlights the importance of preventive measures, to ensure adequate levels of vitamin D in the general population. Vitamin D deficiency is now recognized as a public health care issue, probably due to an ongoing trend of lower amount of time spent for outdoor activities. Vitamin D deficiency is a frequent finding among the whole population[45], with a prevalence that varies significantly across ages, and a consistent trend towards more severe forms in the elderly. Recommendations concerning longer exposure to sunlight and prescription of oral vitamin D supplements or fortified foods, might be a reasonable approach for preventing or correcting hypovitaminosis D. Supplementation of vitamin D might help in preventing infections in the whole population, boosting their immune response, and modulating excessive inflammatory reactions through down regulation of IL-6 production. Indeed, strong evidence on the relationship between low levels of vitamin D and high levels of proinflammatory cytokines, such as IL-6, may suggest a positive immunomodulatory effect of vitamin D in pathologies that involve excessive IL-6 release. In the western countries, more attention should be paid to the vitamin D requirements of all categories of people at high-risk, who are prone to hypovitaminosis D. In summary, there is increasing evidence to support the use of oral vitamin D, especially during this global pandemic, when it might be of great support in the management and control of the COVID-19 infection.

Conflict of Interests

The authors B.O. and V.U. are employees of Lo.Li. Pharma S.r.l. The other authors have nothing to declare.

References

1) Márquez EJ, Chung CH, Marches R, Rossi RJ, Nehar-Belaid D, Eroglu A, Mellert DJ, Kuchel GA, Banchereau J, Ucar D. Sexual-dimorphism in human immune system aging. Nat Commun 2020; 11: 751.
2) Zhang L, Liu Y. Potential interventions for novel coronavirus in China: a systematic review. J Med Virol 2020; 92: 479-490.
3) Lippi G, Nouvenne A, Ticinesi A, Bonelli P, Salvagno GL, Cervellin G, Guidi GC. The burden of vitamin D deficiency in a mediterranean country without a policy of food fortification. Acta Biomed 2015; 86: 59-62.
4) Edwards MH, Cole ZA, Harvey NC, Cooper C. The global epidemiology of vitamin D status. J Aging Res Clin Prac 2014; 3: 148-158.
5) Spiro A, Buttriss JL. Vitamin D: An overview of vitamin D status and intake in Europe. Nutr Bull 2014; 39: 322-350.
6) Albahrani AA, Greaves RF. Fat-soluble vitamins: Clinical indications and current challenges for chromatographic measurement. Clin Biochem Rev 2016; 37: 27-47.
7) Harrison HE. Parathyroid hormone and Vitamin D. Yale J Biol Med. 1966; 38: 393-409.
8) Monastra G, De Grazia S, De Luca L, Vittorio S, Unfer V. Vitamin D: a steroid hormone with progesterone-like activity. Eur Rev Med Pharmacol Sci 2018; 22: 2502-2512.
9) IOM (Institute of Medicine). Dietary reference intakes for calcium and vitamin D. Washington, DC: The National Academies Press 2011.
10) Pramyothin P, Holick MF. Vitamin D supplementation: guidelines and evidence for subclinical deficiency. Curr Opin Gastroenterol 2012; 28: 139-150.
11) Botella-Carretero JI, Alvarez-BlascobJuan F, Villafruela JJ, Balsa JA, Vázquez C, Escobar-Morreale HF. Vitamin D deficiency is associated with the metabolic syn-

drome in morbid obesity. Clin Nutr 2007; 26: 573-580.

12) Ding C, Gao D, Wilding J, Trayhurn P. Vitamin D signalling in adipose tissue. BJN 2012; 108: 1915-1923.

13) Nair R, Maseeh A. Vitamin D: the "sunshine" vitamin. J Pharmacol Pharmacother. 2012; 3: 118-126.

14) Chun RF, Liu PT, Modlin RL, Adams JS, Hewison M. Impact of vitamin D on immune function: lessons learned from genome-wide analysis. Front Physiol 2014; 5: 151.

15) Wei R, Christakos S. Mechanisms underlying the regulation of innate and adaptive immunity by vitamin D. Nutrients 2015; 7: 8251-8260.

16) Carvalho JTG, Schneider M, Cuppari L, Grabulosa CC, Aoike TD, Redublo QBM, Batista CM, Cendoroglo M, Moyses RM, Dalboni MA. Cholecalciferol decreases inflammation and improves vitamin D regulatory enzymes in lymphocytes in the uremic environment: A randomized controlled pilot trial. PLoS One 2017; 12: e0179540.

17) Xie Z, Chen J, Zheng C, Wu J, Cheng Y, Zhu S, Lin C, Cao Q, Zhu J, Jin T. 1,25-dihydroxyvitamin D3-induced dendritic cells suppress experimental autoimmune encephalomyelitis by increasing proportions of the regulatory lymphocytes and reducing T helper type 1 and type 17 cells. Immunology 2017; 152: 414-424.

18) Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020; 46: 846-848.

19) Labudzynskyi D, Shymanskyi I, Veliky M. Role of vitamin D3 in regulation of interleukin-6 and osteopontin expression in liver of diabetic mice. Eur Rev Med Pharmacol Sci 2016; 20: 2916-2919.

20) Hashemi R, Morshedi M, Asghari Jafarabadi M, Altafi D, Saeed Hosseini-Asl S, Rafie-Arefhosseini S. Anti-inflammatory effects of dietary vitaminD3 in patients with multiple sclerosis. Neurol Genet 2018; 4: e278.

21) Adegoke SA, Smith OS, Adekile AD, Figueiredo MS. Relationship between serum 25-hydroxyvitamin D and inflammatory cytokines in paediatric sickle cell disease. Cytokine 2017; 96: 87-93.

22) Beilfuss J, Berg V, Sneve M, Jorde R, Kamychev E. Effects of a 1-year supplementation with cholecalciferol on interleukin-6, tumor necrosis factor-alpha and insulin resistance in overweight and obese subjects. Cytokine 2012; 60: 870-874.

23) Manion M, Hullsiek KH, Wilson EMP, Rhame F, Kojic E, Gibson D, Hammer J, Patel P, Brooks JT, Baker JV, Sereti I; Study to Understand The Natural History Of Hiv/Aids In The Era Of Effective Antiretroviral Therapy (The 'Sun Study') Investigators. Vitamin D deficiency is associated with IL-6 levels and monocyte activation in HIV-infected persons. PLoS One 2017; 12: e0175517.

24) Dalvi SM, Ramraje NN, Patil VW, Hegde R, Yeram N. Study of IL-6 and vitamin D3 in patients of pulmonary tuberculosis. Indian J Tuberc 2019; 66: 337-345.

25) Krivoy A, Satz J, Hornfeld SH, Bar L, Gaughran F, Shoval G, Hochman E, Weizman A, Taler M. Low levels of serum vitamin D in clozapine-treated schizophrenia patients are associated with high levels of the proinflammatory cytokine IL-6. Int Clin Psychopharmacol 2020; 35: 208-213.

26) Liao H, Pan LL, Du J, Wang T. Relationships between the levels of serum 25-hydroxyvitamin D and interleukin-6 in patients with Takayasu's arteritis. Zhonghua Yi Xue Za Zhi 2018; 98: 3509-3512.

27) Song J, Xu S, Zhang ZH, Chen YH, Gao L, Xie DD, Sun GP, Yu DX, Xu DX. The correlation between low vitamin D status and renal interleukin-6/STAT3 hyper-activation in patients with clear cell renal cell carcinoma. Steroids 2019; 150: 108445.

28) Karimi S, Tabataba-Vakili S, Ebrahimi-Daryani N, Yari Z, Karimi A, Hedayati M, Hekmatdoost A. Inflammatory biomarkers response to two dosages of vitamin D supplementation in patients with ulcerative colitis: a randomized, double-blind, placebo-controlled pilot study. Clin Nutr ESPEN 2020; 36: 76-81.

29) Lacroix M, Lizotte F, Hivert MF, Geraldes P, Perron P. Calcifediol decreases interleukin-6 secretion by cultured human trophoblasts from GDM pregnancies. J Endocr Soc 2019; 3: 2165-2178.

30) Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, Li J, Zhao D, Xu D, Gong Q, Liao J, Yang H, Hou W, Zhang Y. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020; 395: 809-815.

31) Yu N, Li W, Kang Q, Xiong Z, Wang S, Lin X, Liu Y, Xiao J, Liu H, Deng D, Chen S, Zeng W, Feng L, Wu J. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. Lancet Infect Dis 2020; 20: 559-564.

32) Paradisi R, Porcu E, Venturoli S, Maldini-Casadei M, Boni P. Maternal serum levels of proinflammatory cytokines in missed and threatened abortion. Am J Reprod Immunol 2003a; 50: 302-308.

33) Paradisi R, Maldini-Casadei M, Boni P, Busacchi P, Porcu E, Venturoli S. T-helper 2-cytokine levels in women with threatened abortion. Eur J Obstet Gynecol Reprod Biol 2003b; 111: 43-49.

34) Szekeres-Bartho J, Falkay G, Török A, Pacsa AS. The mechanism of the inhibitory effect of progesterone on lymphocyte cytotoxicity: II. Relationship between cytotoxicity and the cyclooxygenase pathway of arachidonic acid metabolism. Am J Reprod Immunol Microbiol 1985; 9: 19-22.

35) Szekeres-Bartho J, Wegmann TG. A progesterone-dependent immunomodulatory protein alters the Th1/Th2 balance. J Reprod Immunol 1996; 31: 81-95.

36) Szekeres-Bartho J, Faust Zs, Varga P. The expression of a progesterone-induced immunomodulatory protein in pregnancy lymphocytes. AJRI 1995; 34: 342-348.

37) Szekeres-Bartho J, Barakonyi A, Par G, Polgar B, Palkovics T, Szereday L. Progesterone as an immunomodulatory molecule. Int Immunopharmacol 2001; 1: 1037-1048.

38) Szekeres-Bartho J, Wilczynski JR, Basta P, Kalinka J. Role of progesterone and progestin therapy in threatened abortion and preterm labour. Front Biosci 2008; 13: 1981-1990.

39) Szekeres-Bartho J, Halasz M, Palkovics T. Progesterone in pregnancy; receptor-ligand interaction and signaling pathways. J Reprod Immunol 2009; 83: 60-64.

40) Szekeres-Bartho J, Miko E, Balassa T, Unfer V. Society for Maternal Fetal Medicine and the American Journal Of Obstetrics & Gynecology. Conference 6 Feb, 2020 Dallas. TX, USA.

41) de Sa Del Fiol F, Barberato-Filho S, Lopes LC, de Cassia Bergamaschi C. Vitamin D and respiratory infections. J Infect Dev Ctries 2015; 9: 355-361.

42) Roth DE, Jones AB, Prosser C, Robinson JL, Vohra S. Vitamin D receptor polymorphisms and the risk of acute lower respiratory tract infection in early childhood. J Infect Dis 2008; 197: 676-680.

43) Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, Goodall EC, Grant CC, Griffiths CJ, Janssens W, Laaksi I, Manaseki-Holland S, Mauger D, Murdoch DR, Neale R, Rees JR, Simpson S Jr, Stelmach I, Kumar GT, Urashima M, Camargo CA Jr. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. Br Med J 2017; 356: i6583.

44) Berry DJ, Hesketh K, Power C, Hyppönen E. Vitamin D status has a linear association with seasonal infections and lung function in British adults. Br J Nutr 2011; 106: 1433-1440.

45) De Rui M, Toffanello ED, Veronese N, Zambon S, Bolzetta F, Sartori L, Musacchio E, Corti MC, Baggio G, Crepaldi G, Perissinotto E, Manzato E, Sergi G. Vitamin D deficiency and leisure time activities in the elderly: are all pastimes the same? PLoS One 2014; 9: e94805.