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**Combined use of lactoferrin and vitamin D as a preventive and therapeutic supplement for SARS-CoV-2 infection: Current evidence**

Cipriano M *et al*. Lactoferrin and vitamin D against SARS-CoV-2 infection

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**ABSTRACT**

Lactoferrin is a multifunctional protein that exhibits anti-inflammatory, immunoregulating and anti-infective properties. One of its receptor sites is located on SARS-CoV-2. The binding of lactoferrin with heparin sulfate proteoglycans may prevent initial contact between the virus and host cells, thus preventing subsequent infection. Given that lactoferrin may act as a natural mucosal barrier, an intranasal treatment together with its oral intake can be hypothesized to prevent the spread, infection and inflammation caused by COVID-19. The literature reports that vitamin D plays an essential role in promoting an immune response. With its anti-inflammatory and immunoregulatory properties, vitamin D is critical for activating the immune system’s defenses, improving immune cell function. Different studies also demonstrate that lactoferrin is a potential activator of the vitamin D receptor. Combined use of lactoferrin (through an association of oral intake and nasal spray formulation) and vitamin D could be valuable for COVID-19 treatment and prevention. However, further randomized clinical trials are needed before recommending/prescribing them.

**Key Words:** Lactoferrin; Vitamin D; SARS-CoV-2; COVID-19; Pandemics

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**Core tip:** Combined use of lactoferrin, using a nasal spray formulation in association with its oral intake, and vitamin D could be valuable for treatment and prevention of COVID-19.

**INTRODUCTION**

Lactoferrin is a glycoprotein that is contained in human secretions, and is part of a nonspecific defense system with a significant role in fighting bacterial and viral infections, in addition to producing significant anti-inflammatory effects on various mucosal surfaces and acting in the regulation of iron metabolism[1]. However, the biological activities of lactoferrin have been attributed only in part to its iron-sequestering activity[2], given that its mechanism of action also involves binding to other specific receptors, cell signaling and protein folding[3,4]. Lactoferrin can directly interact with virus capsid proteins[5], which may hinder viral entry into target cells by blocking the virus from binding to host cell components that are used as receptors or coreceptors.

Direct binding of lactoferrin to viral particles has been recognized for many viruses[6-9]. In this sense, a protective role of lactoferrin could also occur in relation to SARS-CoV-2 infection[10,11]. In this review, we discuss evidence for the potential clinical and molecular effects of lactoferrin (alone or in combination with another supplement) in the prevention or treatment of COVID-19.

**SCIENTIFIC FINDINGS SUPPORTING THE ROLE OF LACTOFERRIN IN SARS-COV-2 INFECTION**

In the current scientific landscape, special attention has been paid to the potential role of lactoferrin as a supplemental adjuvant, whether in terms of preventing SARS-CoV-2 infection or treating COVID-19, due to its ability to interact with different receptors. Results of recent research show that the cellular entry of the virus occurs via high-affinity interactions between the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein and the human host angiotensin-converting enzyme 2 (ACE2) receptor[12]. However, for cellular entry of the virus, there must also be interaction of SARS-CoV-2 with other molecules, including heparan sulfate and cell proteases (such as lysosome-localized cathepsin B/L and serine proteases of the TMPRSS family). This is essential to virus adhesion to the cell membrane, which may facilitate the interaction of the viral spike protein with the ACE-2 receptor, as well as internalization of SARS-CoV-2[13-15].

In particular, the binding of lactoferrin with heparin sulfate proteoglycans (HSPGs) may prevent initial contact between the virus and host cells, thus preventing subsequent infection. In SARS-CoV-2 infection, HSPGs play an important role in the cell entry process, as the anchoring sites provided by HSPGs allow the initial interaction between SARS-CoV-2 and host cells, and the concentration of viral particles on the cell surface. In other words, the virus, by binding to HSPGs, rolls across the cell membrane and scans specific entry receptors, thus enhancing the ability of the virus to infect the host cell[16].

Computational studies[17] have sought explanations for a direct interaction between lactoferrin and the ACE2 receptor or between lactoferrin and the viral spike protein, identifying possible reciprocal interactions that may provide a molecular explanation for the preventive effect of lactoferrin against SARS-CoV-2 infection. Lactoferrin has the ability to bind to the ectodomain of ACE2 with high affinity. In contrast, there is no binding to RBD up to the maximum physiological concentration range of lactoferrin. This suggests that the inhibitory effect of lactoferrin on the formation of the ACE2/RBD complex may be related to its binding to the ACE2 receptor, thus weakening the evidence of binding to the RBD of the spike protein[18].

Based on data from the animal and human studies, Zimecki *et al*[19] postulated that lactoferrin may have a clinical benefit in preventing and ameliorating the COVID-19-induced cytokine storm and its devastating consequences on lungs and other vital organs. Kell *et al*[20] suggest a similar process. More precisely, lactoferrin is capable of performing two functions in cases of SARS-CoV-2 infection: on the one hand, it sequesters iron and inflammatory molecules that significantly increase during the cytokine storm; on the other hand, it helps to occupy receptors (ACE2/RBD) and HSPGs, preventing the virus from binding to host cells. Receptor blockade is an important peculiarity of lactoferrin when used as a supplement. Lactoferrin may help prevent thrombocytopenia and hypercoagulation, which are major complications of COVID-19.

Studies with swabs for SARS-CoV-2 detection demonstrated that there are higher levels of viral RNA in the upper airways than in the throat, in both symptomatic and asymptomatic patients. This suggests that the nasal epithelium may be an important site for initial infection, acting as a key reservoir for viral spread through the respiratory mucosa[12]. In light of this, it could be hypothesized that local treatment of the nasal mucosa with lactoferrin in a nasal spray formulation or through its oral intake may counteract SARS-CoV-2 infection and inflammation. Lactoferrin has the ability to serve as a natural barrier of the respiratory and intestinal mucosa, and its inclusion in preservative structures (liposomes) may reduce gastric and intestinal denaturation, which is critical to maintaining its integrity and biological functionality. Such findings suggest that lactoferrin could be a supplement for use in both asymptomatic and mildly symptomatic patients to prevent exacerbation of COVID-19[21].

**MYELOID-DERIVED SUPPRESSOR CELLS VERSUS COVID-19: ACTION OF LACTOFERRIN**

Recent research has verified the presence of a dysregulated myeloid cell compartment containing an increased number of myeloid-derived suppressor cells (MDSCs) in severe COVID-19 patients, which may be correlated with disease severity. The mechanism of action of MDSCs involves promoting the survival of SARS-CoV-2 through the suppression of T-cell responses, leading to a highly proinflammatory state in response to secretion of mediators of immune activation[22]. MDSCs are defined as bone-marrow-derived innate immune cells with the ability to suppress effector T-cell responses. This heterogeneous population of cells is composed mainly of two distinct subtypes that include polymorphonuclear or granulocytic MDSCs, and monocytic MDSCs. Among their roles is the ability to regulate a wide variety of adaptive (T and B cells) and innate (including natural killer cells, macrophages, and dendritic cells) immune cells[23].

Results of an important study that evaluated the effect of lactoferrin on MDSCs show that MDSCs from mice and human infants are sensitive to lactoferrin, whereas the same is not true of adult MDSCs. To explain the rationale for this reduced sensitivity, the authors also assessed the expression of different receptors capable of binding to lactoferrin, such as lipoprotein receptor-related protein (LRP)-1, LRP2, intelectin (ITLN)-1 and ITLN2. MDSCs from newborn mice were found to have stronger expression of LRP2 compared to ITLN1, ITLNb or LRP1. Another finding of interest was that the expression of LRP2 decreased with age, resulting in a substantial reduction in LRP2 expression on the cell surface[24]. This may, in addition to explaining differences in the sensitivity of MDSCs to lactoferrin between infants and adults, serve as evidence to understand more about the molecular peculiarities of COVID-19 in different age groups, in order to propose more appropriate preventive and/or therapeutic protocols.

**EVIDENCE FOR COMBINED USE OF LACTOFERRIN AND VITAMIN D**

In light of the benefits that seem to be associated with the use of lactoferrin in COVID-19 patients, it may be useful to conduct further studies on the potential benefits of a combination of lactoferrin with others nutraceuticals to verify the possible synergistic effects in the fight against SARS-CoV-2 infection. In recent years, research on vitamin D has been extensive and evolving, demonstrating that there is an important interaction between vitamin D and cells of the innate and adaptive immune systems. Regarding the role in supporting innate immunity, serum 25-hydroxyvitamin D [25-(OH)D] bound to vitamin-D-binding protein allows intracellular entry of free [25-(OH)D] into antigen-presenting cells (APCs). This results in endogenous production and the action of 1-α, 25-dihydroxyvitamin D [1,25(OH)2D] through the vitamin D receptor (VDR), leading to the induction of antimicrobial proteins like cathelicidin, nuclear factor kappa β, and β-defensins that may contribute to the elimination of SARS-CoV-2[26].

In this context, the innate immune system is expected to fight the viral infection first until the adaptive immune system (T and B cells) is sufficiently activated, which usually occurs within 7–10 d after the primary infection. SARS-CoV-2 infection causes the activation of APCs that can induce SARS-CoV-2 phagocytosis, through communication with naïve T cells. An optimal serum vitamin D level may lead to differentiation of naïve T cells into T helper (Th) 2 cells instead of Th1 cells, promoting the production of anti-inflammatory cytokines such as interleukin (IL)-10, IL-5, and IL-4. Anti-inflammatory cytokines have the ability to decrease the secretion of proinflammatory cytokines, including interferon-γ, IL-6, IL-2 and tumor necrosis factor-α, by downregulation of Th1 cells. All this may result in an important anti-inflammatory reaction with potential to control the over-reaction of the immune system against COVID-19[25].

In the presence of vitamin D deficiency, the adaptive immune response shifts towards differentiation of naïve T cells into Th1 cells, which may cause hyperinflammation/cytokine storm[25]. According to Prietl *et al*[26], numerous cells (including immune cells) possess enzymes that metabolize vitamin D. This process appears to be critical for normal immune function, and altered or insufficient levels of vitamin D may cause dysregulation of immune responses. In an important review article, four potential mechanisms by which vitamin D may affect T-cell function were proposed: direct endocrine effects on T cells mediated by systemic calcitriol; direct intracrine conversion of 25(OH)D to calcitriol by T cells; direct paracrine effects of calcitriol on T cells following conversion of 25(OH)D to calcitriol by monocytes or dendritic cells; or indirect effects on antigen presentation to T cells mediated by localized APCs affected by calcitriol[27].

Two recent studies have evaluated the effects of lactoferrin on vitamin D. The first demonstrated that lactoferrin is a potential activator of the VDR through expression of VDR mRNA, postulating that lactoferrin directly targets the cell nucleus to regulate VDR transcription activity in vitamin-D-deficient mice. Lactoferrin appears to show an affinity for three specific DNA sequences that appear similar in the VDR promoter. Thus, the authors of this study hypothesize that lactoferrin regulates VDR expression by binding directly to these DNA elements and that it may act as a transcription factor or coactivator to stimulate VDR expression[28]. In the other study, Wang *et al*[29] demonstrated that lactoferrin, in addition to having a protective role in the intestine in mice deficient in vitamin D and reducing elevated serum proinflammatory cytokines, also has the ability to stimulate, increasing the expression of VDR.

**CONCLUSION**

Combined use of lactoferrin and vitamin D could be valuable for treatment and prevention of SARS-CoV-2 infection. In addition, the association of oral intake of lactoferrin and a nasal spray formulation would be an additional tool to prevent the spread and worsening of the infection. Although the combined use of lactoferrin and vitamin D seems to be a promising approach as an adjuvant for COVID-19 management, there are still no *in vivo* studies with robust evidence to prove the benefits of using this combination of supplements against SARS-CoV-2 infection. Further randomized clinical trials are needed to show any related beneficial action before recommending/prescribing them for the population[30]. With the exception of the use of approved drugs, what is known so far is that the practice of physical exercises may be an ally for COVID-19 prevention and treatment, as well as to enhance SARS-CoV-2 vaccine immunogenicity[31].

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