

Effect of Lactoferrin as Supportive Treatment for Coronavirus Disease on Oral Health: A Narrative Review

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ABSTRACT

Lactoferrin (LF) is an extremely preserved, pleiotropic, iron-binding glycoprotein of the transferrin family produced and released by glandular cells and is present in most bodily fluids. Research suggests that LF may be used to manage or avert various microbial illnesses; also, it's been proven that LF can be considered a supportive treatment for coronavirus disease-19 (COVID-19). Lactoferrin is a nonheme iron-binding glycoprotein strongly expressed in human and bovine milk, and it plays many functions during infancy, such as iron homeostasis and defense against microorganisms. In humans, LF is mainly expressed in mucosal epithelial and immune cells. This review aims to highlight the multifunctional activities of Lf on general and oral health. In this study, 144 articles were selected based on their titles and abstracts across many electronic databases including PubMed, Science Direct, Google Scholar and Scopus by providing an overview about the mechanisms related to LF intrinsic synthesis and discussing the large variety of its physiological functions such as iron homeostasis, immune regulation, oxidative stress, inflammation, and apoptosis while specifying the mechanisms of action. Finally, we will focus on its recent physiopathology implications in the management of coronavirus disease and its relation to dental caries and periodontitis. In conclusion, Lactoferrin may be a crucial nutrient to support host immunity, acting as an antiviral and antibacterial agent, especially keeping in mind the COVID-19 pandemic.

KEYWORDS: Lactoferrin, iron, oral health, dental caries, periodontal disease.

1. INTRODUCTION

The worldwide transmission of the coronavirus disease-19 (COVID-19) virus has been caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). One noticeable and recurring finding is the variation in COVID-19 severity among different age groups. Severity, the necessity for hospitalization, and death rate grow sharply with age whereas severe sickness and death are comparatively uncommon in children and young people [1, 2, 3].

1.1. The Impact of (COVID-19) on Oral Health

Substantial COVID-19 acute infection and related treatment interventions may have a detrimental effect on oral health, possibly resulting in xerostomia, gingivitis, ulcerations, and other opportunistic fungal infections due to compromised immune function and/or susceptible oral mucosa [4].

Oral signs and symptoms involved white patches, hemorrhagic crust, tissue necrosis, petechiae, edema, erythema, ulceration, erosion, bulla, vesicular lesions, pustule, cracked or depapillated tongue, macule, papule, plaque, discoloration, bad breath, and accidental bleeding. Aphthous stomatitis, herpetiform lesions, candidiasis, vasculitis, Kawasaki-like, Erythema Multiforme-like, mucositis, necrotizing periodontal disease, and angular cheilitis were among the suggested diagnoses for oral lesions. In descending order, the tongue (38%), labial mucosa

(26%), palate (22%), gingiva (8%), buccal mucosa (5%), oropharynx (4%), and tonsil (1%), were the most frequently involved areas. In 68% of the cases, oral lesions were symptomatic, causing pain, burning sensations, and itching. The interval between the onset of systemic symptoms and the development of oral lesions ranged from 4 days to 12 weeks [5].

Symptomatic treatment involving Pain relievers (acetaminophen or ibuprofen), antipyretics for fever alleviation, cough syrups are used to treat patients with mild symptomatic illness. It's also advised to get sufficient rest, maintain healthy eating and drinking habits, and drink plenty of water to keep the body well-hydrated and nourished. For patients whose disease progresses quickly, corticosteroid medication, neutralizing antibody therapy, gene therapy and cell therapy may be employed as appropriate treatment [6, 7]. The Food and Drug Administration (FDA) has authorized immunomodulators (such as lactoferrin), neutralizing antibody treatments, cell therapy, and gene therapy [7].

1.2. Multifunctional Activities of Lactoferrin

Lactoferrin (LF) is a naturally produced, beneficial glycoprotein that has been tested for its ability to fight a range of viruses. Its ability to modulate immunity and reduce inflammation can strengthen the body's defenses against infections [8]. It works against severe acute respiratory disease coronavirus (SARS-CoV), which is intimately associated with the recently discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that triggers COVID-19 [9].

Thus, it is conceivable that LF, similarly in the case of SARS-CoV, can prevent SARS-CoV-2 infiltration at micromolar levels and in a dose-dependent way [10]. Since the immunomodulatory and anti-inflammatory properties of LF play a significant role in its biological activity, the degree of inflammation and immune system reaction in viral infections, especially, could frequently have an impact on how severe the illness is, this is especially true for COVID-19 [11].

1.3. Role of Lactoferrin in Management of Iron Deficiency anemia in Children

Bovine Lactoferrin is a safer and more effective alternative than elemental iron for treating iron deficiency and iron deficiency anemia, as it is proved that oral administration of bovine lactoferrin (BLF) significantly increases the number of red blood cells, hemoglobin, serum ferritin and total iron after thirty days of the treatment [12].

2. METHODOLOGY

To conduct this narrative review on methods to determine the effect of orally supplemented lactoferrin on enamel surface a search strategy was conducted in May 2024 across many electronic databases including PubMed, Science Direct, Google Scholar and Scopus. Papers and articles were searched from 2002 to 2024 using MeSH term/keywords such as 'Lactoferrin', 'Hardness', and 'Enamel'. Only articles published in English were selected. Initially, 144 articles were selected based on their titles and abstracts. Only full-text articles were selected to conduct this review. After full text evaluation, removing duplicates, conducting a quality assessment of selected articles based on PRISMA checklist and application of the eligibility criteria, 30 articles were selected to conduct the review Fig. 1.

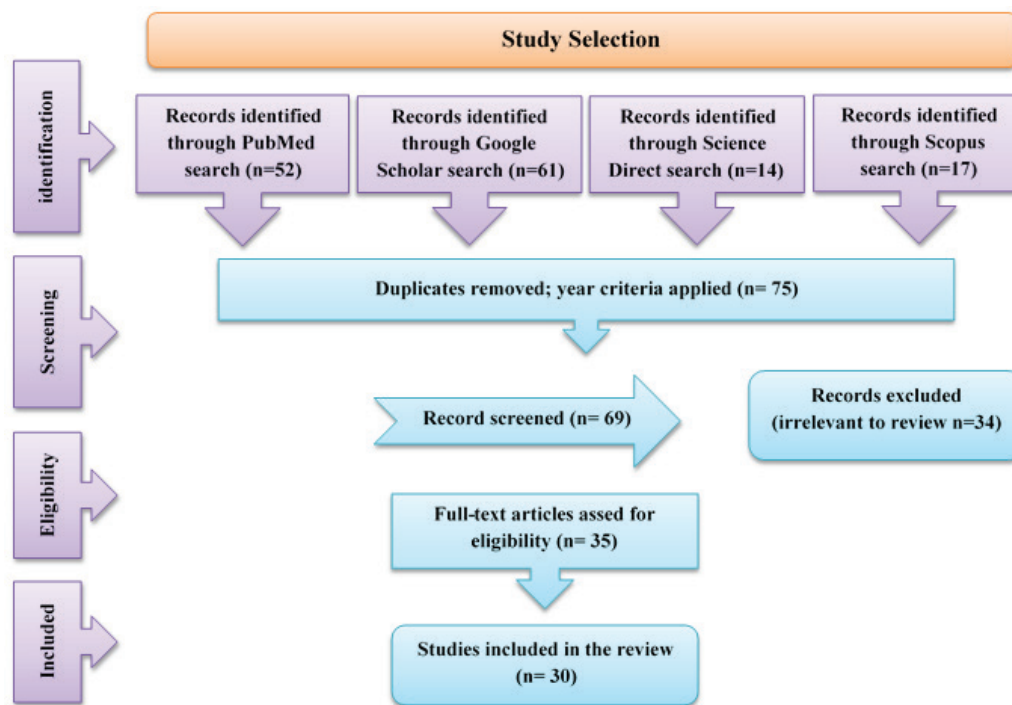


Fig. 1: Flowchart showing the articles selection process to conduct this review.

2.1. Overview About Relation of Lactoferrin and Oral Health

2.1.1. Lactoferrin

Lactoferrin (LF) or lactotransferrin has lately gained attention, especially in relation to the novel coronavirus pandemic which started in 2019 (COVID-19). The body's capacity to fight infection is positively impacted by diet and vitamins, which also maintain a healthy immune system [13].

2.1.2. Biology of Lactoferrin

LF is an extremely preserved, pleiotropic, iron-binding glycoprotein of the transferrin family that is produced and released by glandular cells and is present in most bodily fluids [13]. It is an 80 kDa glycoprotein with a well-characterized main structure made up of 703 amino acid groups. Since its identification, LF and its associated peptides have primarily been regarded as significant non-specific host defense chemicals against a range of pathogens, including viruses like the herpes simplex virus, cytomegalovirus and human immunodeficiency virus (HIV) [14].

2.1.3. Sources of Lactoferrin

- It has been present in particularly elevated levels in mammalian milk and was initially discovered in bovine milk and was later separated from human milk [15 ,16]. The body secretes lactoferrin through exocrine glands, which are responsible for producing tears or maternal milk, and human neutrophil secondary granules [13].
- It can be consumed as a dietary supplement, where it then serves as nutraceutical or functional food like bovine lactoferrin or in form of tablets as immune care, strongImmune or even in form of sachets [17].

2.1.4. Concentrations of Lactoferrin in the Human Body

Mature milk has less lactoferrin than colostrum milk, and it's also found in the majority of exocrine secretions (Table 1) and the secondary granules of mature neutrophils. In areas of infection or inflammation, the concentration of lactoferrin rises because of the neutrophil recruitment [18, 19]. It is produced and released by neutrophils and glandular epithelial cells, with the greatest concentrations (~ 8 mg/mL) present in human colostrum [20].

Table 1: Lactoferrin Levels in Human Secretions [21].

Biological fluids	Concentration (mg/mL)
Colostrum	8
Milk	1.5-4
Saliva	0.008
Tears	2
Vaginal secretion	0.008
Seminal fluid	0.112
Joint fluid	0.001
Plasma	0.0004
Cerebrospinal fluid	Undetectable

2.1.5. Properties of Lactoferrin

Recently, LF's anti-inflammatory and immunomodulatory functions have drawn more attention from scientists because it seems to be able to control how the body reacts to infections and can both activate the immune system to fight pathogenic invasion and prevent negative host immune and inflammatory reactions [11].

LF is also widely known for its antibacterial, antiviral, antifungal, anti-inflammatory, immunomodulatory, and anti-carcinogenic properties. Some data suggesting that LF may be a crucial nutrient to support host immunity were gathered, acting as an antiviral and antibacterial agent, but especially keeping in mind the COVID-19 pandemic [17].

2.1.6. Lactoferrin and Oral Health

Multiple studies showed that low lactoferrin levels can prevent dental biofilm growth. The capacity of lactoferrin to sequester or chelate iron necessary for biofilm formation was identified as the cause of the lactoferrin impact rather than interfering with bacterial cell proliferation [22]. Dental plaque is a multispecies biofilm made up of both Gram-positive and Gram-negative bacteria that grows successively in a metabolically interactive fashion [23]. Dental caries-associated biofilms usually contain high concentrations of acidogenic, Gram-positive bacteria, whereas biofilms associated with periodontitis are often more diverse in composition but contain high concentrations of Gram-negative bacteria [24, 25].

2.1.7. Effect of Lactoferrin on Dental Caries

It is investigated how bovine lactoferrin affects acid production and demineralization of dental enamel utilizing *Streptococcus mutans* in a culture system and a synthetic mouth modeling system. A radial diffusion experiment was used to assess the antibacterial effect of bovine lactoferrin (BLF) against *S. mutans*. A batch culture was utilized to investigate the impact of BLF on the production and adhesion of water-insoluble glucan, as well as the attachment of *S. mutans* to a glass surface in the culture system. The quantity of synthetic biofilm, the pH variations beneath the biofilm, and the alterations in the microhardness of the enamel determined by a Vicker's Hardness Tester were assessed. The levels of water-insoluble glucan in a firm-adherent fraction were dramatically reduced by 0.1–1.0% BLF. Compared to

the control group, the BLF group's microhardness alterations on enamel slabs revealed a noticeably smaller hardness reduction. BLF had no effect on the artificial biofilm buildup. Based on the study's findings, it appears that BLF may prevent *S. mutans* from fermenting acids and demineralizing enamel [26]. The impact of baby formulae on the adherence of bacteria associated with dental caries was evaluated by an in vitro investigation focused on the capacity of *Lactobacillus gasseri* and *Streptococcus mutans* to bind saliva-coated hydroxyapatite beads coated in formulas with varying concentrations of iron and lactoferrin. A round-bottom microtiter plate was used to hold reservoirs containing radiolabeled *Lactobacillus gasseri* or *Streptococcus mutans* along with saliva obtained from children aged 0 to 5 years old. The hydroxyapatite assay (HA-assay) was used to test the bacteria's binding capacity. Their findings showed that formula 5, which most likely contains Lf, had the strongest ability to prevent *L. gasseri* and *S. mutans* from binding HA-beads. This is likely partially because Lf has protective features. Similarly, the results showed that formula 1, which most probably does not contain Lf, had less power to prevent the same bacterium from adhering [27].

The effect of human Lactoferrin (hLF) administration was evaluated in lactoferrin-knockout (LFKO^{-/-}) mice infected with *S. mutans*. Mice were assessed for colonization, salivary pH, and caries development. The results showed that the lactoferrin-knockout infected (LFKO^{-/-}I) mice had significantly higher colonization with *S. mutans* ($P = 0.02$), lower salivary pH ($P = 0.01$), and more carious lesions ($P = 0.01$) when compared to wild-type infected (WTI) mice. In addition, the administration of hLF did not show any evidence of *S. mutans* colonization as well as carious lesions ($P = 0.001$) in LFKO^{-/-}I mice when compared to untreated LFKO^{-/-}I mice. So, it's concluded that the endogenous LF protects against *S. mutans*-induced caries and that the exogenous hLF can exert a protective effect against caries development [28]. Carious lesions in 20 permanent third molars were treated with a combination of hydroxyapatite and the enzymes lysozyme, lactoferrin, and lactoperoxidase. Carious dentin was collected and homogenized in a vortex shaker. After homogenization, five decimal dilutions were performed. Three aliquots of 25 μ L of each dilution were seeded onto the surface of mitis salivarius bacitracin (MSB) medium. All plates were incubated in anaerobic jars. After incubation, the viable bacterial count was determined. *S. mutans* counts were obtained before and 24 h, 1 month, and 6 months after treatment. It is shown that the combination of hydroxyapatite with lysozyme, lactoferrin, and lactoperoxidase may be an alternative for *S. mutans* control in dentinal caries, which was evaluated by measuring viable *Streptococcus mutans* [29].

2.1.8. Effect of Lactoferrin on Periodontitis

The reduction of Lf levels in saliva and GCF following surgical periodontal therapy in cases of chronic periodontitis was reported [30]. Lactoferrin is not produced by healthy gingival tissues, and increased levels of Lf in the GCF of inflamed gingival tissues arise from infiltrating inflammatory cells [31]. When healthy individuals participated in experimental gingivitis, a similar Lf drop in GCF and peripheral blood was also observed following dental hygiene procedures [32]. Although lactoferrin concentrations in gingival crevicular fluid are greater than in normal persons, they are equivalent in patients with gingivitis and periodontitis. Hence, LF, a possible component of the host's defense, is produced by neutrophils in GCF against periodontopathic bacteria and considered as a useful indicator of periodontal disorders [21].

A study was conducted to assess how oral lactoferrin (LF) and lactoperoxidase (LPO)-containing tablets affected periodontal health. Seventy-two patients with chronic periodontal disease were randomized to receive either control tablets or tablets containing bovine LF and LPO. Gingival crevicular fluid (GCF) was assessed at baseline, one week, four weeks, and twelve weeks for periodontal parameters and concentrations of subgingival plaque bacteria, bovine and human LF, and endotoxin. Over the duration of the investigation, significant variations in the GCF concentrations of bovine LF were noted between the study and control groups. Even so, at one week to twelve weeks, the levels of the clinical and bacteriological parameters were similar in the two groups. Thus, the impact of orally supplemented LF and LPO-containing pills may be insignificant on the study's periodontal and bacteriological profiles [33].

2.1.9. Effect of Lactoferrin on Enamel Surface

An in vitro study investigated the effect of orally supplemented Lactoferrin on 80 samples of primary and permanent teeth enamel by immersion of the teeth samples into Lactoferrin suspension for 30 days. It's found that lactoferrin suspension decreased the microhardness of enamel and both calcium and phosphorus weight percentages. Both dentitions exhibited erosions in the enamel surface, with primary teeth being more affected than the permanent teeth [34].

2.2. Lactoferrin as a Potential Preventive and Adjunct Treatment for COVID-19

The commonly recognized "viral surfing" model explains the function of cell surface heparan sulphate proteoglycans (HSPGs) by having invasive virus particles "surf" from low affinity HSPG anchoring sites to high-affinity entry receptors during an invasion. This model is supported by the similarity in spike protein structures between SARS-CoV and SARS-CoV2, as well as the fact that both viruses rely on the same angiotensin-converting enzyme 2 (ACE2) receptor to enter cells [35, 36]. Hence, it is reasonable to speculate about a comparable process in which HSPGs act as SARS-CoV-2 attachment sites, aggregating the virus on the cell surface and enabling particular entrance receptors like ACE2. That means that, similar to SARS-CoV, Lf probably has the ability to block SARS-CoV-2 invasion at micromolar levels and in a dose-dependent way [10]. Seventy-five symptomatic SARS-CoV-2-positive individuals showed a 100% recovery in 4-5 days when treated with orally supplemented liposomal bovine lactoferrin containing 32 mg of LF given four to six times a day for ten days in combination with zinc 10 mg two to three times daily, as well as the same medication at a lower dosage seemed to protect healthy individuals from the illness [37]. The immunomodulatory and anti-inflammatory properties of LF are another important component of its bioactivity. These properties are especially important when it comes to viral infections, as the degree of inflammation and immune response can frequently determine how severe a disease becomes. This is especially true with COVID-19 [11].

It is proposed that the cause of COVID-19 mortality is not only viral infection, but in some cases, cytokine storm syndrome linked to hyperinflammation that causes severe respiratory distress and ultimately death. In severe COVID-19 patients, the cytokine profile is characterized by elevated levels of cytokines and acute-phase reactants like tumor necrosis factor-alpha (TNF α), ferritin and interleukin 6 (IL-6) [38]. A preliminary in vivo investigation was carried out to examine the antiviral efficacy of oral and intranasal liposomal bovine LF (BLF) in individuals with mild-to-moderate COVID-19 who were asymptomatic. Thirty-two patients (fourteen being hospitalized and eighteen being isolated at home) were given only oral

and intranasal liposomal BLF. Twenty-eight patients isolated in their homes did not take any medicine, whereas twenty-two hospitalized patients received just standard care treatment. Those with COVID-19 treated with liposomal BLF recovered from their symptoms more quickly than those with standard of care treatment. Significant reductions in serum ferritin, IL-6, and D-dimers were seen in patients receiving BLF. There were no negative outcomes noted. These findings suggest a possible role for BLF in the treatment of COVID-19 individuals who are asymptomatic and mildly to moderately infected [39].

In vitro experiments were conducted and, demonstrated that LF directly attaches to both SARS-CoV-2 and cell surface molecules to produce an antiviral effect against SARS-CoV-2. It's interesting to note that the in-silico findings provided compelling evidence for the theory that LF and the spike S glycoprotein directly recognize each other, thereby restricting the ability of the virus to enter cells and they assumed a possible additional role for LF in the care of COVID-19 patients as a result of these in vitro data [40]. The effectiveness of BLF and lactoferricin B, a proteolytic component of BLF, was assessed against several potentially dangerous SARS-CoV-2 variants. An in vitro investigation revealed that bovine lactoferrin demonstrates broad antiviral properties against SARS-CoV-2 variants. Multiple dairy-based proteins and bioactive peptide sources were examined for antiviral actions; however, antiviral action was found to be specific for BLF and associated with the BLF content in dairy components. Its therapeutic importance may be increased by the minimal anti-SARS-CoV-2 activity of lactoferricin B, a breakdown product of BLF. BLF's capacity to inhibit SARS-CoV-2 was not affected by the typical additives used in tablet production, sorbitol and dextrose. Going forward, BLF appears to be a good option for studying against SARS-CoV-2 due to its availability, tolerability, and in vitro performance [41].

3. CONCLUSION

Lactoferrin's anti-inflammatory and immunomodulatory functions have drawn more attention from scientists because it seems to be able to control how the body reacts to infections and can both activate the immune system to fight pathogenic invasion and prevent negative host immune and inflammatory reactions.

Lf is also widely known for its antibacterial, antiviral, antifungal, anti-inflammatory, immunomodulatory, and anti-carcinogenic properties. Some data suggesting that Lf may be a crucial nutrient to support host immunity were gathered, acting as an antiviral and antibacterial agent, but especially keeping in mind the COVID-19 pandemic.

4. RECOMMENDATIONS

The following could be deduced within the constraints of the present article:

- 1- Further in-vitro studies are recommended for further investigations, like evaluating the effect of orally supplemented lactoferrin on different restorative materials.
- 2- Further in vivo studies are also recommended for further investigations.

CONFLICT OF INTEREST

There was no conflict of interest.

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APPENDIX A: LIST OF ABBREVIATIONS

ACE-2	Angiotensin converting enzyme 2
BLf	Bovine Lactoferrin
COVID-19	Coronavirus disease-19
FDA	Food and Drug Administration
GCF	Gingival Crevicular Fluid
IL1	Interleukin-1
Lf	Lactoferrin
SARS-CoV	Severe acute respiratory syndrome- Coronavirus
SARS-CoV-2	severe acute respiratory disorders coronavirus-2
TNFα	Tumor necrosis factor-alpha
WHO	World Health Organization