



Review article

Therapeutic properties of lactoferrin

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ABSTRACT

Introduction: For many years, milk and colostrum proteins have been the object of scientists' interest. A group of whey proteins, including lactoferrin (Lf) are credited with special features that promote health and wellbeing.

Aim: The purpose of this paper is to disseminate health and medical properties of lactoferrin originating from the cow's milk and bovine colostrum.

Discussion: Extensive research (clinical as well) proves that lactoferrin is beneficial for the human organism. Moreover, no harmful side-effects have been reported following its application. Effective antibacterial function against intestinal pathogenic bacteria and simultaneous stimulation of beneficial microflora are the main functions of this compound. Lactoferrin can also be used in management of cancer and numerous viral infections (i.e. herpes virus or rotavirus) as it stimulates the immune system.

Conclusions: In summary, lactoferrin is a milk protein increasingly more appreciated in medicine. Interest in this protein is rising, which is reflected in numerous scientific and clinical studies that underline its medical importance. Furthermore, research will surely contribute to the understanding of its function and ultimately, it will play a significant role on the market.

1. INTRODUCTION

Recently, milk and colostrum proteins, as well as their derivatives, have become the objects of scientists' interest. Beside obvious nutritional functions, it is mainly because of their biological role.^{1–4} Colostrum and milk are the most complete and wholesome of all meals – especially to a newborn.^{5,6} It is because of the health supporting properties of the protein, which on average accounts for 4% of milk composition.⁷ The principle milk protein is casein, but it is its allergenic properties that are mostly emphasized on.^{8,9} On the contrary, whey proteins are praised for their exceptional functions. They comprise an average of 20%–25% out of total protein content.^{2,4,10} They are composed of α -lactalbumin, β -lactoglobulin, plasma albumin, as well as: immunoglobulins, lactoperoxidase, lysozyme and lactoferrin.¹¹ The above-mentioned proteins are detrimental for the correct immune reaction of the organism. Therefore, more and more food preparations for newborns, convalescents or athletes are enriched by those proteins.¹²

2. AIM

The aim of this paper is to underline the properties of lactoferrin and its application in medicine, on the basis of current scientific and overview data. Special attention was paid to the prophylactic values of lactoferrin and its use in treatment of various diseases.

3. DISCUSSION

3.1. Short characteristic of lactoferrin

Recently, significance of bovine colostrum in functional products has diametrically increased.¹³ It is all due to lactoferrin (Lf), which content in colostrum is significantly higher than in milk.^{14,15} Lactoferrin is a secreted protein, present in milk and colostrum, but also in body fluids as well as tears and saliva. Its content in bovine milk ranges 50–120 mg/dm³.¹⁰ Whereas Zander et al.¹⁶ present the following content range: 0.1–0.3 mg/cm³, which stands for 1% of total whey protein content. Lactoferrin name is derived from Latin. *Lac* – means milk, whereas *lacto* – milky and *ferrum* – iron. Thus, milk protein of high affinity to iron was created.¹⁷ Lactoferrin is a glycoprotein, built from 689 amino acids, which molecular weight is about 80 kDa. It consists of a single polypeptide chain with two homological lobes. Each of these lobes has one binding area that can coordinate with one iron ion on the third degree of oxidation (Fe³⁺).^{17–19} Through chelating abilities, lactoferrin lowers the availability of iron to pathogens.²⁰ It stops their growth as well.^{21,22} Complexes of lactoferrin with ions such as: Ga³⁺, Al³⁺, Mn²⁺, Cu²⁺, Co³⁺ have been reported so far.¹⁷

Biologically active peptides, which can be obtained by the enzymatic cutting of lactoferrin, are possible to be distinguished.²³ The cut is performed thanks to the enzymatic di-

gestion of lactoferrin by pepsin. In result the created peptide is called lactoferricin.^{24,25}

3.2. General lactoferrin properties

Lactoferrin is the so called immunoregulator. This means that its function involves inducing growth of precursor T-cells into mature helper cells as well as differentiation of immature B-cells.¹⁸ In result B-cells become cells effectively producing antigens.²⁶ Beside the fact of immune system stimulation, antibacterial, antiviral, anti-inflammatory and antifungal properties are worth noting. It is also credited with anticancer features. Lactoferrin is described by scientists as a multipotential protein.^{16,17,28}

3.3. Antibacterial activity

Antibacterial activity of lactoferrin can be direct (damage of cell walls or change in bacterial metabolism) or indirect (stimulation of organism's defense – faster response to infection).⁶ Especially the effective antibacterial activity is shown in case of *Escherichia coli* strain or other pathogenic intestinal bacteria. At the same time, it stimulates the activity of beneficial microflora of *Bifidobacterium* species (selective lactoferrin activity).²⁹ Furthermore, lactoferrin increases sensitivity of bacteria to some antibiotics (vancomycin, penicillin) and influences the decrease of their effective doses. For example, as Diarra et al.¹⁴ report the combination of penicillin with lactoferrin doubled the inhibitory activity of antibiotic against *Staphylococcus aureus*. Defensive activity of lactoferrin was presented in systemic infection of mouse with *S. aureus*, while whey protein was used as an addition to drinking water (in the amount of 2%). A decrease in bacterial count in kidneys 5–12 times was observed.³⁰ Additionally, Haversen et al.³¹ proved that in case of urinary tract infections with *E. coli* in mice, lactoferrin and its peptides were found in urine 2 hours after oral intake. It is highly suggestive that lactoferrin may be active at the infection site as well. Trumpler et al.³² clinically confirmed the effectivity of lactoferrin in alleviating the course of infection in patients with neutropenia to whom chemotherapy was applied.

3.4. Antiviral properties

The presence of sialic acid and modification of compound structure that appears during iron ions binding process (as well as manganese and zinc) may have an impact on antiviral lactoferrin activity. Herpes virus (HSV), human immunodeficiency virus (HIV), hepatitis type B and C virus (HCV) or rotavirus all turned to be sensitive to lactoferrin activity.^{6,33} Zimecki and Artym⁶ underline that the synergistic activity of lactoferrin (as well as lactoferricin) with some antiviral compounds may lower the dose of applied medications, which are toxic to organism. Synergistic activity was observed during lactoferrin application with acyclovir in Herpes Simplex-1 (HSV-1) infection. It allowed to lower the dose of medication 2–7 times.³⁴ Nozaki et al.³⁵ showed simi-

lar effects using lactoferrin and interferons (IFN) in HCV infections of people. Lactoferrin can be used as a selective drug carrier because it has an ability to penetrate to the cellular viral receptors.^{6,32}

3.5. Anticancer properties

Lactoferrin and its peptide – lactoferricin effectiveness in the treatment of cancer is confirmed by *in vitro* and *in vivo* studies. Eliassen et al.³⁶ state that lactoferrin had a significant antiviral activity directly on cancer line cells of fibrosarcoma, melanoma and colon cancer. Zimecki and Artym⁶ confirm the cytotoxic activity of lactoferrin. Mechanism includes damage to cell membrane and lysis of cell *in vitro*, what reduces tumors *in vivo*. In Shimamura et al.³⁷ studies lewis lung carcinoma cells were applied to mice thus inducing angiogenesis, after which the lactoferrin was applied to them which inhibited tumor growth. Such function of lactoferrin results from the direct inhibitive impact on endothelial proliferation as well as indirect impact on IFN release.

3.6. Immuno-stimulating activities

Multipotential protein has also the fundamental function in immune system – it stimulates immune response. As studies conducted on several experimental models by Zimecki et al.³⁸ report, lactoferrin has been applied to New Zealand Black mice for several months, in which the autoimmunological hemolytic disease has been developing and it caused lowering of positive Coombs reaction percentage. It means that IgG antibody titers engaged in autoimmunological reactions decreased.³⁸ Additionally, after the pre-incubation of peritoneal lymphocytes of examined mice with lactoferrin, the decrease in number of erythrocyte antigen recognizing cells was noticed.^{6,38}

One of very interesting aspects connected with the discussed protein is the fact that lactoferrin alone can act as an analgesic agent or can cooperate with morphine.³⁹ Analgesic activity of lactoferrin is mediated by nitrous oxide. Earlier statements confirm studies conducted on mice by Narayan Raju et al.⁴⁰ Authors report that after reversal of lactoferrin activity by the opioid receptor antagonist (naloxone) the inhibition of psychical stress symptoms in the examined animals was observed. What is more, the analysis of formalin test in rats confirmed the effectiveness of increase of morphine analgesic activity.³⁹

4. CONCLUSIONS

1. Lactoferrin has been an object of scientists' interest for several years. First of all, its popularity was gained by the high content in bovine colostrum but also many invaluable properties. Surely, next decade will bring further studies which will allow to use it and its derivatives potential to full extent.

2. Lactoferrin is a multipotential protein which isolated from milk or colostrum is effective, safe and easily digested. Therefore, it can be used with many substances creating products that can be easily used in treatment but also in prevention of some diseases.
3. Thanks to chelating abilities, lactoferrin has a number of antibacterial, antiviral, anticancer properties as well as directly and indirectly influences human immune system. Thankfully to its selectivity, it inhibits pathogenic bacteria growth, simultaneously creating good environment for growth of proper intestinal microflora. It is worth to underline the possible use of lactoferrin as an analgesic substance.

Conflict of interest

None declared

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