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NUTRITION

Lactoferrin Immunity Benefits in Infant Health

Lactoferrin supporting early life immunity

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Introduction

- **Human breastmilk is the gold standard reference for infant formula development. When considering the protein component, breastmilk informs the total content, amino acid profile and composition of minor proteins. Minor proteins such as lactoferrin are often at higher concentrations in human milk than cow's milk.**
- **Lactoferrin is known for its role in natural defence mechanisms, especially its anti-microbial and immune modulating benefits.**
- **Lactoferrin also has antioxidant properties, anti-inflammatory effects, may facilitate iron absorption and may have a prebiotic effect to support healthy gut microflora.**
- **SureStart™ Lactoferrin can be used to increase the content of lactoferrin in infant formula.**

Human breast milk is the ideal source of nutrients to support healthy growth and development of infants. In addition, breast milk contains an abundance of bioactive components that are highly likely to be of physiological significance. In particular, there are unique biochemical and immunological factors that provide protection to the infant against infection.

When breastfeeding isn't possible, human milk substitutes such as infant formula are considered the only safe alternative by the World Health Organisation[1,2]. However, it is accepted that several outcomes of breastfed infants are superior to those of formula-fed infants, both in the short and long term. Breastmilk composition is the gold standard reference when manufacturing infant formula[3].

Human milk contains bioactive proteins, lipids, and carbohydrates that stimulate intestinal development, actively protect the infant from pathogenic infection, and facilitate the establishment of the microbiota[4-6]. Significantly, early life immunity is characterized by impaired functions of innate (natural) and adaptive (acquired) immune responses. This immune status makes newborns more susceptible to infections and allergic diseases. One of the critical roles of breast milk is to protect the vulnerable newborn against subsequent infection by both directing correct maturation of the innate and adaptive immune systems, and by delivering components with direct anti-microbial activities[3,7-9]. One of the key components in human milk that may have roles in both immune system maturation and as an anti-microbial agent is lactoferrin.

Human milk and cow's milk are compositionally different including both the total level of protein and the composition of the individual protein components (Table 1).

Table 1.
Protein Content in Human and Cow's Milk[10-13]

Protein	Human Milk (g/L)	Cow's Milk (g/L)	Typical Infant Formula (g/L)
Total protein	9-11	33	15
Casein	3-5	26	6
Whey Protein	4-6	5-7	9
ß-lactoglobulin	-	3-4	4.5
α-lactalbumin	3-4	1	1.2
Serum albumin	0.3	0.4	-
Immunoglobulins	0.6-1.2	0.7	-
Lactoferrin	1-3	0.1-0.4	0.01-0.1[1]

1. Theoretical level in unfortified IF assuming Lf is ~1% of whey protein and upper level of fortified IF

One of the most abundant proteins in human milk is lactoferrin but it is present at only minor levels in bovine milk. The reported typical breastmilk lactoferrin content is about 1-3 g/L (Table 1). The lactoferrin concentration in human milk has been reported to be consistent across different ethnicities and geographies (Figure 1[14]). The concentration of lactoferrin declines with time over lactation both in human milk (concentrations ranging from 6 g/L in early milk (<28 days lactation) to 2 g/L in mature milk)[15,] and bovine milk (ranging from 0.8 g/L in colostrum to 0.1 g/L in mature milk)[16], as has been seen with other major milk proteins.

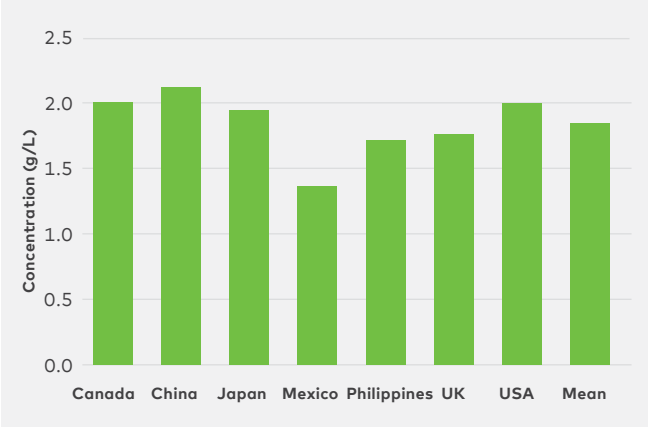

Figure 1. The concentration of Lactoferrin in Human Milk[14]

LACTOFERRIN

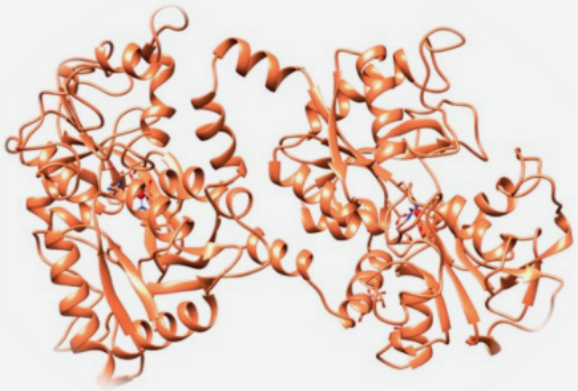

Image from Giansanti et al 2016. doi: 10.3390/ph9040061

Lactoferrin is a multifunctional iron-binding glycoprotein of the transferrin family[17,18] that occurs naturally in milk with partial iron saturation (15-20% saturated). Iron binding gives lactoferrin its characteristic pink colour[1]. Human and cow's milk lactoferrin have a high degree of similarity[19,20], although human lactoferrin has a lower level of iron saturation. Lactoferrin is also present in many other biological fluids such as tears, saliva, and other secretions, and is thought to play an important role in defence against microbial invasion[17].

BIOLOGICAL ROLES OF LACTOFERRIN

There have been many studies and reviews published describing the functions and roles of lactoferrin[21-24]. These functions include:

- Anti-bacterial and anti-viral activity
- Anti-inflammatory properties
- Enhancement of gut mucosal immunity and protection
- Anti-oxidant properties
- May help absorption of iron from the diet
- Prebiotic effect

Many studies have shown that lactoferrin functions as a prominent component of the first line of host defence against infection and may be important for the protection of the vulnerable newborn with an immature immune function[25]. Lactoferrin has a broad range of anti-microbial activities against a range of bacterial, viral and fungal pathogens[26-28]. It is now known that several mechanisms contribute to the broad-spectrum anti-infective and anti-inflammatory roles of lactoferrin[29,30]. These include the ability of lactoferrin to bind iron making it unavailable to pathogenic microorganisms therefore preventing their growth and proliferation[31,32]. Several peptides generated during lactoferrin digestion have also been shown to have potent anti-microbial properties[33,34]. Additionally, lactoferrin possesses indirect activity, often through prevention of pathogen invasion by blocking interaction with receptors used for entry on host cells[35,36].

Further research suggests that lactoferrin's ability to provide immune protection may also be due to other immune-modulating and anti-inflammatory properties that may enhance gut mucosal immunity and protection[37-41]. In vitro and in vivo studies suggest the existence of multiple mechanism that include immune cell recruitment, modulation of chemokine/cytokine production and the regulation of production of reactive oxygen species. These studies also suggest that lactoferrin may affect both innate and adaptive immune responses and modulate both acute and chronic inflammation[21,37-43].

Lactoferrin is a mediator that naturally bridges the innate and adaptive immune functions by regulating target cell response, including those involved in oxidative stress and systemic inflammatory responses. It is also recognised as a significant contributor in regulation of antigen presentation and development of productive T helper cell response[44].

Results from in vitro and in vivo studies show that lactoferrin is capable of interacting with a range innate immune cells responsible for front line immunity, including granulocytes, lymphocytes, macrophages and natural killer (NK) cells, thereby enhancing their functions such as proliferation, maturation, migration, cytokine production and cytotoxicity[45-49].

Lactoferrin can also affect cells of the adaptive immune system[50-53]. Lactoferrin may promote the differentiation of immature B-cells into efficient antigen-presenting cells (APCs) and may assist the maturation of T-cell precursors into competent T helper cells. Lactoferrin can change the balance of Th1 and Th2 cellular subsets that helps limit excessive inflammatory responses[54].

Lactoferrin also enhances immunoglobulin secretion in the gut, proliferation of immune cells and increases the production of immune regulating messengers in the gut[33,55,56].

Finally, lactoferrin may also mediate iron absorption in the gut. Receptors have been identified in the gut which can bind to lactoferrin facilitating iron absorption into the cells[57]. Some animal model studies have supported the hypothesis that lactoferrin facilitates iron absorption but convincing evidence from infant studies is lacking[58], although two recent studies do report the ability of lactoferrin to improve iron status in infants[59,60].

HUMAN EFFICACY STUDIES OF LACTOFERRIN

Although the outcomes from human studies have been variable[61] the strongest evidence from human studies is for a protective role of lactoferrin against infection.

A recent infant clinical study in healthy infants aged 5+ months given lactoferrin-supplemented infant formula for 3 months reported a significant reduction in respiratory tract infections and symptoms (Figure 2) using a dose of 38mg/100g powder[62]. An earlier randomised trial in infants fed infant formula containing 85mg lactoferrin/100ml (~600mg/100g powder) resulted in fewer respiratory tract infections and improved iron status[59]. A study in older infants (12-18 months) given lactoferrin (0.5g twice a day) showed a decrease in the longitudinal prevalence and severity of diarrhea, but not in incidence[63].

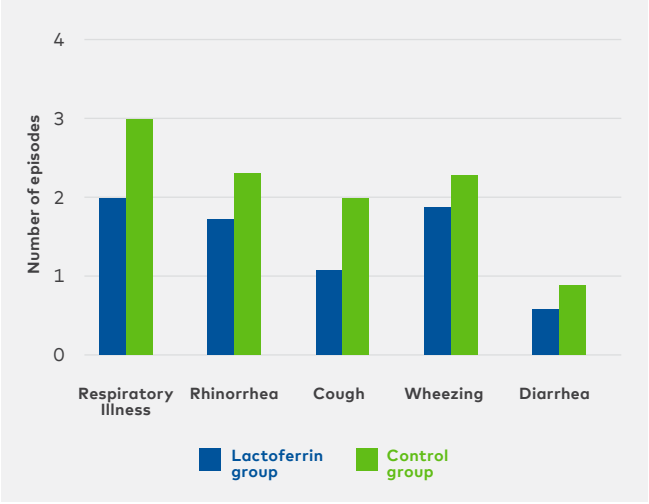

Figure 2. Morbidity episodes* in infants fed control or bovine lactoferrin-containing infant formula[62]
*all effects were statistically significant p<0.05

A very recent study in 4 month old Kenyan infants showed that apo-lactoferrin (non-iron saturated lactoferrin), 1.41g, added to a test meal containing $FeSO_4$ significantly increased iron absorption (+56%) compared to a meal without apo-lactoferrin[60].

Lactoferrin has also been shown in studies with preterm infants to promote the growth of beneficial gut bifidobacteria, thus helping to establish a microflora balance that is important for a healthy immune system[10,64,65]. A more recent study showed that high levels of fecal lactoferrin in neonates, particularly in the first days of life, could represent an important factor in the initiation, development and/or composition of the neonatal gut microbiota[66].

However other studies have not reported the same prebiotic effect, so further work is needed in this area to determine the role that lactoferrin plays in the development of a healthy gut microflora. Since early host-microbe interaction is a crucial component of healthy immune and metabolic programming, high levels of fecal lactoferrin in neonates may beneficially contribute to the immunologic maturation and well-being of the newborn, especially in pre-term infants.

Further insights on the immune protection benefits of lactoferrin come from studies in vulnerable populations. Analysis of pooled data from two studies on preterm infants (<2500g[67] and <2000g[68] birth weight) given 200mg/kg/d of bovine lactoferrin for 4 weeks concluded that lactoferrin had a protective effect against the risk of development of late-onset sepsis, particularly in infants <1000g and among infants with low human milk intake[69]. In another study, lactoferrin supplementation in preterm infants reduced the relative risk of late onset sepsis by up to 80% in non-mothers milk fed infants[70]. Recent systematic reviews and meta-analyses found that lactoferrin supplementation not only reduced the rate of any late onset sepsis in preterm infants, but also reduced the risk of infection and necrotising enterocolitis[71,72]. However, other studies have shown contradictory results. In the ELFIN study in very preterm infants no effect of lactoferrin on infection, mortality or morbidity was found[73]. Another study in very preterm infants also found no effect of lactoferrin on mortality and morbidity, although lactoferrin might reduce late-onset sepsis[74].

There are several reasons why lactoferrin supplementation trials may have inconsistent results. Some possibilities are differences in the population enrolled, the quality and bioactivity of the lactoferrin used, the lactoferrin dose used, the outcome determinations and the presence of other confounding variables not adequately measured.

Overall, the combination of lactoferrin's bioactive properties for immune defence and for gut protection and health support its addition to cow's milk based infant formula to more closely match the levels in human milk.

SAFETY OF COW'S MILK DERIVED LACTOFERRIN INGREDIENTS

Lactoferrin can be extracted and concentrated from cow's milk and used as an ingredient in a number of applications including paediatric nutrition. The lactoferrin is generally 90-95% pure and is then either freeze-dried or spray-dried for dry-blending into infant formula or other powdered nutritional products. Studies have shown that with the right processing conditions, freeze-dried and spray-dried lactoferrin have minimal heat damage and denaturation, and retain excellent solubility[75].

Several studies using cow's milk derived lactoferrin demonstrate the safety of these ingredients for use in infant formula[76]. Cow's milk derived lactoferrin was accepted by the USFDA as a substance Generally Recommended As Safe (GRAS) in August 2001, and was approved as a novel food for use in infant formula by the European Commission in 2012.

CONSUMER INSIGHTS

Lactoferrin is most commonly found in baby foods in the Asia Pacific region where there has been an increasing number of launches of infant formula and baby foods containing added lactoferrin over the last 10 years[77]. Consumer research in China, 2016,[78] found that 64% of female users of infant milk formula had heard of lactoferrin and of those 50% associated lactoferrin with enhancing baby's immunity (Figure 3). A similar level of awareness was reported more recently[79] with 28% of parents associating lactoferrin with immunity and protection. 53% of parents consider "the more the better" when it comes to lactoferrin[80].

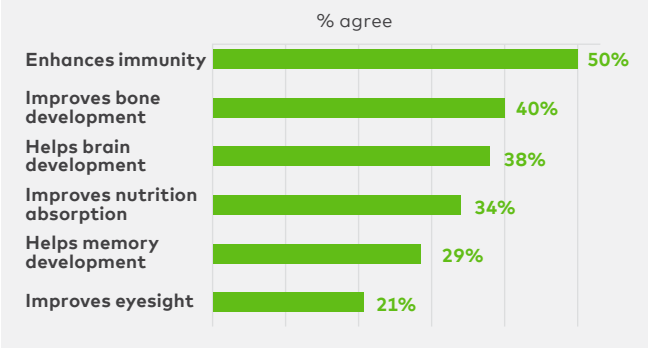

Figure 3. Parents awareness of the benefits of lactoferrin[78]

Base: China: 1,910 female internet users aged 20-39 who are infant formula users who are aware of lactoferrin

Summary

Human milk provides the optimal nutrition for growth, development and immune support, especially needed in the first few months of life. Human milk contains an array of proteins that both supply essential amino acid as well as having bioactive properties. Lactoferrin is one of the most abundant proteins in human milk, and has anti-bacterial and anti-viral properties, making it a useful part of the first line of defence when the immune system is vulnerable. Clinical studies of the bovine Lactoferrin ingredient have shown potential for protection against infection. Therefore, Lactoferrin can be added to infant formula to bring the composition closer to human milk and to provide additional immunity benefits.

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Talk to the paediatric dairy ingredient experts

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