Review Article

The Immunological Benefits of Breast Feeding (Review Article)

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ABSTRACT:

Breast feeding (BF) provides infants with the most suitable nutrients from birth tell weaning. The major part of mother breast milk (MBM) is water in which the other components dissolve. These components include nutrients and immune factors. The concentration of these components varies by time after delivery. Breast milk even provides infants with various types of bacterial species that contribute for development of infant microbiota.

Components that are regarded important for shaping of infant immune response include different factors. MBM contains oligosaccharides which are associated with guts defenses, cytokines that participate in inflammation and immune cells activation, immunoglobulins that arm infant's intestinal mucosa with defense lines against microbial infections. Extracellular micro vesicles (EV) are microparticles with phospholipid bilayer secreted by maternal cells. These particles are highly found inside human milk and they regulate intracellular signaling, inflammation and immune response. Lactoferrin are protein molecules found in human breast milk and play a great role in immune modulation and interaction with different types of microorganisms.

Childs who are breast fed have less incidence of being a victim of auto immune diseases as multiple sclerosis, rheumatoid arthritis or diabetes type. Breast milk has an important effect in protection of infants against several types of bacterial, viral, fungal and parasitic pathogens. MBM stays the most suitable food to infants in spite of the progress of infant's formula industry.

KEY WORDS: Breast milk, immunoglobulin, lactoferrin, microvesicles, oligosaccharides.

INTRODUCTION:

Breast feeding (BF) provides infants with the most suitable nutrition from the time of birth. The United Nations Children's Fund and WHO advice mothers for entire BF for their children up to 6 months of age. BF is recommended to continue until the child reaches 2 years of age[1].

Nourishing components of Mother breast milk (MBM):

Water is the major component of MBM constituting nearly 88% of whole milk in which the other components dissolve. MBM provides infant with the required carbohydrates, protein, fat, minerals and vitamins[2].Components of MBM varies by time after delivery. In the first 2-4 days after birth, it is thick and low in amount (300-400 ml per day) with high concentration of proteins, known as Colostrum. Colostrum provides infant with important immunological factors such as immunoglobulins, lactoferrin, and oligosaccharides. This Colostrum has more importance for protection of preterm delivered infants who expresses deficiencies in innate, adaptive, humoral and cellular immune response[3]. Later on, these components levels decline with more increase of nutritional components in MBM as carbohydrates, fats, vitamins and minerals. However, MBM continues as a source of cytokines, hormones, growth factors, adrenomedullin anti-microbial peptides, microbiota, immunoglobulins and different enzymes[4,5]. Research works showed that these ingredients have direct and indirect effect on the infection rate by different infectious agents (bacteria, viruses, and parasites); and also, modulate the immune system affecting the development of various autoimmune diseases[3,4].

Breast milk microbial flora:

Breast milk contains various types of bacteria species that gives antimicrobial and probiotics effect. The main bacteria found in breast milk includes *Bifidobacterium, Lactobacillus, Staphylococcus, Streptococcus, and Enterococcus.* These microbiotas are the main source of intestinal normal flora of the infants[1, 6]. Different hypothesis was stated to explain the presence of these microbiota in MBM as the "enteromammary hypothesis which stated that these microbes passed from between mother intestinal lining cells and find their way to the breast glands, other states that these bacteria passed retrogradely from infant mouth and maternal skin during feeding to the milk canals inside the mother breasts[1]. These intestinal microbes have a crucial effect on the future development of the immune system which affects both childhood and adult life. Their potential effect is mainly noticed on the development of allergic, and chronic inflammatory disease especially the one affecting the bowel, diabetes mellitus and even on the response to vaccination[7] .

Human Oligosaccharides in breast milk (HMOs):

They are types of molecules that have brought considerable attention. They present in about 0.6-4.5 w/v of human breast milk[8] . MBM have a larger amounts and more complex structures oligosaccharides than other mammalian milk[9]. MBM provides infant with oligosaccharides named gangliosides in form of disialogangliosides in colostrum and monosialogangliosides in the next released milk. Evidences suggest that these HMOs have different functions in improving the newborn defense mechanisms specially those associated with guts defenses. From these suggested functions: First, they promote the growth of milk microbiota specially Lactobacilli and *Bifidobacterium*[10]. They provide the infant gut flora with an additional support by providing different oligosaccharides that act as bifidogenic factors that help 200 beneficial intestinal bacterial strains to grow. HMOs play important role in early formulation of normal bacterial flora in infant bowel promoting fermentation of lactic acid and modulation of the intestinal immune response[11]. Second, HMOs have a structure resemble the epithelial cell surface glycans of the intestinal epithelia cells and thus function as an analog binding site for the pathogens, preventing intestinal pathogen adhesion to epithelial surfaces by that it decreases the risk of infection[12].

From the microorganisms that HMOs can decrease their risk of infection is *Compylobactor jeujini and Entamoeba histolytica* by means of action as decoy receptors that bound to the micro-organisms and prevent them from binding to the intestinal epithelial cells surfaces, so prevent colonization of these microorganisms and predisposition of infection[1,13,14]. In addition, these saccharides prevent viruses from invading macrophages by competing with the viral antigens to prevent them from binding to the PRRs C-type lectins present on macrophage cell surfaces[11].

Third, milk oligosaccharides improve host defense by modulating immunity and promoting intestinal barrier function[15] .

Cytokines in Breast milk:

Mother cytokines that are components of MBM participate in shaping infant immune response. The source of these cytokines whether pro-inflammatory or anti-inflammatory cytokines may be either from mother circulation or released by MBM leukocytes[16] .

Anti-inflammatory cytokines play vital role in gastrointestinal humoral immune response by promoting differentiation of B lymphocytes and release of different immunoglobins. Presence of pro-inflammatory cytokines may impose adverse effects as induction of systemic inflammation specially in case of high levels of TNF alpha, on the other hand presence of IL-8 may promote immune cells chemotaxis that may protect against gastrointestinal and respiratory infectious agents[17]. Many other cytokines are confirmed in-breast milk or in colostrum as IL-1 alpha, Il-2 receptor antagonist, macrophages migration inhibitory factors, colony stimulating factors, SDF-1 alpha, CTAK/CCL-27, MCP3/CCL7 and LIF. All these factors are important for immunomodulation and protection against autoimmune diseases [18].

Immunoglobulins of Breast milk:

Immunoglobulins provided through breast milk to the infant arm infants intestinal mucosa with defense lines against microbial infections. Specific immunity including secretory IgM and secretory IgA in addition to IgG are provided to infant with breast milk. These immunoglobulins do not traverse mucosal surfaces; therefore, they stay on the luminal surfaces of intestinal mucosa. These antibodies decrease respiratory and gastrointestinal tract infections[19]. Secretory IgA antibodies provided by mother to infant have wide cross reactivity. These antibodies chelate microbes and bring antigens to the antigen presenting cells APCs which initiate with the submucosal T cells an exclusion process to differentiate commensal from pathogenic microbes, so preventing translocation between commensals and microbes. The mechanism of differentiation between microbes and commensals still obscure. Data from different published works show that deficiency of sIgA predispose to dysbiosis in infant's intestine[7,20]

Extracellular Microvesicles (EV):

They are about 50 to 265 nm microparticles that included a phospholipid bilayer-enclosed particles which are secreted by cells to outside and also known as ectosomes[21]. These particles are highly found inside human milk and they regulate intracellular signaling, inflammation and immune response[22]. They also affect the function of intestinal lining cells by enhancing intestinal stem cell activity and proliferation, which provide an effective mechanism in preventing necrotizing enterocolitis in infants[23] and also promote hemostatic stability of the blood[21] .

Human milk lactoferrin:

Lactoferrin among the most important protein component of human breast milk that plays a great role in immune modulation and interaction of different types of infecting microorganisms [24,25]. The concentration of these 78 KDa transferrin like glycoprotein in human milk is variable depending on the time of milk production with highest concentration (5g/L) in the colostrum and lower concentration (2g/L) one month later and continue to decrease over time till one year. Reasons beyond this variation are obscure, however ethnicity, family inheritance, economy, feeding habits of mother fetal maturity at birth and pattern of birth in addition to fetal infections and sepsis may have implications on lactoferrin concentration in MBM[26] .

The lactoferrin modulates effectively the inflammatory and immune responses and their main function is to bind to specific promoter site that regulates the expression of many genes and cytokine production [27]. These proteins have a remarkable activity against infectious agents including bacteria, virus and fungi [24].

Breast feeding and Autoimmune diseases:

Research data shows that MBM have a protective effect against auto immune diseases as multiple sclerosis, rheumatoid arthritis or diabetes type 1[28]. Meta analysis done by Dogaru and his colleagues found that breast fed infants showed 22% less chance of developing pediatric asthma[29]. Studies concerning diabetes type 1, celiac disease, allergic diseases, rheumatic diseases concluded that breast fed babies are of lower risk to develop these diseases than bottle fed ones [30]. Breast feeding influences severity of autoimmune diseases, for example clinical presentation of juvenile arthritis is lower in those with past history of breast feeding in comparison to bottle fed babies[31].Regarding Celiac disease more than one study correlates between reduction in incidence or postponing herald of disease later in life which may be due to direct effect of breast milk immune modulators on autoimmunity of the babies or due to late administration of gluten containing food to the babies as they depend exclusively on breast milk in first 6 months of life[32,33].

Breast feeding and infections:

The breast milk anti-infective agents can play a role in protection against several types of bacterial, viral, fungal and parasitic pathogens by exerting their activities through direct and indirect mechanisms. The main role in protection is by preventing the adhesion, colonization and internalization of these pathogens. This action is mainly accomplished by action of different breast milk components[34] .HMOs in addition to their probiotic effect on enhancing infant's microflora they compete with the pathogens on their binding site. Human milk glycans, have common epitopes that compete with the viruses, bacteria, parasites or even toxins for binding site on intestinal epithelial cells because these glycans are synthesized by similar glycosyltransferases [35]. For example, milk glycans bind viruses such as HIV and rotavirus, bacteria such as *Vibrio cholerae*, and *Escherichia coli Streptococcus pneumoniae* (Table 1,2).

Other substance such as lactoferrin, EVs, cytokines and mucines also have a a direct antimicrobial effect[35]. Lactoferrin have antibacterial, antiviral, anti-fungal and anti-parasitic activity. Lactoferrins show ability to disrupt bacterial cell membranes, depleting iron from microorganisms and blocking the interaction between viruses and host cells. They demonstrate both bactericidal and bacteriostatic activity against several bacteria, so they will kill some and limit the growth of others[36] as shown in (Table 2).EVs are one of the most important colostrum compounds that have great antiviral activity, a study conducted by Donalisio et al. (2020) demonstrated the great activity of these EVs and their protein surfaces against CMV which may be used in later life to fight virus[37] .

Breast milk lactoferrin also has shown antifungal activity as their antimicrobial activity against *Candida albicans*[38]. In addition to the antibacterial and antifungal activity these breast milk lactoferrin also has antiprotozoal activity[36].

In addition to all these factors breast milk provides infant with the magic immunoglobins that provide infants mucosa with weapons to fight different pathogens, therefore, breast fed babies have less chance of being infected than those who are bottle fed.

Table 1: List of milk components and viruses that HBM decrease their infection rate.

Milk component	Virus	Reference
HMO	*Norovirus*	(46,47)
HMO	*Zika virus*	(48,49)
Lactoferrin	*HIV*	(50,51)
Lactoferrin	*SARS Cov 2*	(52,53)
Lactoferrin	*Rota virus*	(54,55)
Human milk glucan	*RSV*	(56,57)
Human milk glucan	*CMV*	(56,57)

Table 2: List of milk components and bacteria that HBM decrease their infection rate.

Milk component	**Bacteria**	**Reference**
Lactoferrin	Group B *Streptococcci*	(40)
Lactoferrin	*Streptococcus pneumoniae*	(44)
HMO	EPEC *E. coli*	(58,59)
HMO	*C. jejuni*	(14)
HMO	*Vibrio cholerae*	(60)
HMO	*L.monocytogenes*	(60)
Lactoferrin	*Pseudomonas aeruginosa*	(24)

CONCLUSION:

MBM has various constitutional parts with different concentration depending on their production time these parts like HMO, lactoferrin, cytokines, EV, immunoglobulins can affect human defense mechanisms and modulate the immune system, helping the infants to fight different infectious agents and prevent autoimmune diseases [19].

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