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Immunomodulatory Effects of Human Colostrum and Milk

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ABSTRACT

The immune system is not fully developed in human neonates and infants; breastfeeding is important in this stage as the bioactive components of human breast milk are known to have anti-microbial, anti-inflammatory, and immunomodulatory effects, and can therefore contribute to an infant's immunity against allergies, asthma, autoimmune diseases, and inflammatory bowel disease. Herein, the positive effect on the immune system by human colostrum and milk are reviewed.

Keywords: Human milk; Immune system; Breastfeeding

INTRODUCTION

The mortality rate of breastfed babies at all ages of infancy was reported to be lower even in studies published as early as 1922 [1]. According to a 1968 study by Scrimshaw et al. [2], the mortality rate of artificially fed infants was seven times that of breastfed babies. The high positive influence of breastfeeding on the life span and mortality rate is attributed to the immunomodulatory effects of breast milk.

In a systematic review published in 2003, Jones et al. [3] predicted that exclusive breastfeeding through the first six months could prevent 13% of childhood deaths in children younger than 5 years of age. Notably, the maximization of the immunological effects of breastfeeding is dependent on the dose-response relationship and varies according to breastfeeding exclusivity and duration.

The immune system of a newborn baby is immature at birth and develops more rapidly during the first two years of life. Specifically, the immature neonatal immune system is deficient in its ability to produce B lymphocytes and immunoglobulins and is limited in its systemic cell-mediated immune response. Neutrophil activity is delayed, which renders infants susceptible to bacterial infections. Additionally, several immune components are produced in low or limited quantities, including complements from the complement system/cascade, interferon-gamma (IFNγ), secretory immunoglobulin A (sIgA), interleukins (ILs), tumor necrosis factors (TNFs), lactoferrin, and lysozyme [4]. Thus, the various bioactive and immunomodulatory factors that are present in human milk can complement the development of the mucosal and systemic immune systems of neonates [5,6].

BIOACTIVE FACTORS IN HUMAN MILK

The important components of human milk can be categorized into three main groups: bioactive factors, proteins, and fats. Bioactive factors include nutritional components (macronutrients, lactoferrin, transferrin, vitamin B_{12}-binding protein), hormones (erythropoietin, prolactin, insulin, gonadotropins, ovarian steroids, thyroid-releasing hormone, thyroid-stimulating hormone, etc.), growth factors (epithelial growth factor, insulin-like growth factor, etc.), neuropeptides (neurotensin, somatostatin, bombesin, etc.), cytokines (TNFα, IL-6, etc.), prebiotics, and nucleotides [7,8].

Milk proteins are essentially divided into whey components and casein; the most abundant proteins are casein, lactoferrin, alpha-lactalbumin, sIgA, and lysozyme. The protein content is higher in the milk the from mothers of preterm babies than in the milk from the mothers of term babies [9]. Although milk protein concentration does not change according to the quantity of protein consumed by the mother, it increases with increasing body weight for height of the individual and decreases in mothers with enhanced breast milk production [10].

Human hindmilk contains a 2–3 times higher fat concentration than foremilk, with palmitic and oleic acids making up the major fat types [11]. Milk fat globules (MFGs), which are composed of glycoproteins and lipids, are the second most abundant fat in human milk. These membrane glycoproteins act as antibacterial and antiviral ligands, preventing pathogens from attaching to the intestinal mucosa, thereby protecting the infant from infection [12]. MFGs also contain mucins (MUC1 and MUC4) [13]. MUC1 blocks human immunodeficiency virus (HIV) and rotavirus [14], and both MUC1 and MUC4 block *Salmonella* species and Norwalk virus.

Bioactive factors in human milk originate from diverse sources. Some are produced by the mammary epithelial cells, some by the cells within the milk [15], while others are present in the maternal serum and are transported across the mammary epithelium. Furthermore, the secretion of MFGs into milk by the mammary epithelial cells carry a variety of membrane-bound proteins and lipids [16].

IMMUNOLOGICAL FACTORS

Human milk produced during the early lactation period delivers approximately 10^8 maternal leukocytes to infants per day. The quantity of these cells differs among mothers and has been shown to be correlated with a later diagnosis of cow's milk intolerance in breastfed infants [17].

Approximately 80% of leukocytes in early human breast milk are macrophages that migrate from the bloodstream into the milk through the mammary epithelium. These mononuclear leukocytes have the ability to act as potent breast milk macrophages through phagocytosis of human milk components and their differentiation into dendritic cells that stimulate T-cell activity and can therefore provide powerful protection against pathogens [18]. However, in women that test positive for HIV-1 or human T-cell lymphotropic virus type 1, the activity of these leukocytes can increase the risk of mother-to-infant viral transmission.

Cytokines in human milk can cross the intestinal barrier and influence the immune system activity in newborns. For example, transforming growth factor-beta (TGF-β) regulates

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inflammation and wound repair and prevents allergic diseases [19], whereas granulocyte colony-stimulating factor (G-CSF) beneficially affects intestinal development and the treatment of severe infections [20]. G-CSF is not well absorbed at the intestinal surface and instead increases the villus area, crypt depth, and proliferating cell nuclear antigen index; that is, it acts as a topical intestinal growth factor in infants that have ingested breast milk [21]. Other human milk cytokines (e.g., IL-10 and IL-7) can also cross the intestinal wall, with IL-7, in particular, affecting thymic development [22].

The proinflammatory cytokines in human milk are TNFα, IL-6, IL-8, and IFNγ. Although their quantities in breast milk are very small and decrease during lactation [23], they can still recruit neutrophils and enhance intestinal mucosal development. IL-8 may protect against TNFα-mediated tissue damage [24,25]. Although higher levels of IL-6 and IL-8 were found in patients with mastitis, the elevation in levels were noted only in the affected mammary lobes [26,27]. IFNγ, which enhances the Th1/inflammatory response and suppresses the Th2/allergic response [28], was found to be lower in the colostrum of mothers who suffered from allergies, and the levels of the Th2 cytokines IL-4 and IL-13 in those samples were higher than those in the cells of the colostrum of mothers with no allergies [29].

Infants are also born with an immature acquired/adaptive immune system, and therefore have to rely on maternal antibodies to fight pathogens [30]. sIgA, the predominant antibody in human milk, forms a complex with antigens, whereupon they are taken up by intestinal dendritic cells that recognize the foreign antigen [31]. Although the levels of IgM and IgG are low in human colostrum, IgG later becomes more abundant in breast milk [32].

HUMAN MILK OLIGOSACCHARIDES: PREVENTION OF ALLERGIC DISEASE AND COMPOSITION OF BENEFICIAL MICROBIOTA

A large portion of human milk is made up of human milk oligosaccharides (HMOs) that have no actual nutritional value [33] but can act as prebiotics to enhance the growth of probiotic organisms in the infant gut. The conjugates formed from the HMOs and the proteins of probiotic organisms serve as soluble “decoy” receptors for pathogens on the infant's intestinal surface. HMO structures differ among mothers owing to genetic differences [34]. Because human milk also contains microbial organisms, which can change according to the lactation course and maternal characteristics, HMOs may further influence the bacterial composition of breast milk, and subsequently the intestinal microbiome of the breastfed infant [35].

Enterobacteriaceae and *Staphylococci* first colonize in the neonatal intestines [36], and *Bifidobacteria* and lactic acid bacteria colonize in the intestines later [37]. HMOs promote the colonization and growth of beneficial intestinal bacteria, such as *Bifidobacterium* (*B*) and *Lactobacillus* (*L*) [38,39]. A study reported the effects of HMOs when gut colonization in breastfed and formula-fed infants was compared [40].

Both *B. longum* and *B. bifidum* are the major intestinal bacteria found in breastfed infants and metabolize HMOs. In contrast, *B. adolescentis* is usually observed in the adult intestine and is less effective in metabolizing HMOs [41].

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In contrast to *Bifidobacterium* spp., *Bacteroides* spp. are not specifically adapted to metabolize HMOs [42]. Suitable substrate for commensal gut bacteria leads to growth advantage for these bacteria, increasing proper colonization in the intestine and reducing colonization by pathogenic bacteria [43,44].

Certain pathogenic species, including *Clostridium difficile*, *Enterococcus faecalis*, and *Escherichia coli*, do not use HMOs as their carbohydrate substrate source for growth [45]. However, HMOs actively bind to several pathogenic bacteria, thereby preventing adhesion to the intestinal epithelium, which is the first step of infection [46]. Although the infant formula is supplemented with prebiotic oligosaccharide substances, these added oligosaccharides do not contain effective chemical substances of terminal fucose or sialic acid residues, thus missing the biological function of HMOs [47].

HMOs also enhance mucus production and promote epithelial tight junction integrity, thereby supporting epithelial barrier function and directly affecting immune cell activity in the gastrointestinal tract of neonates. Additionally, HMOs modulate the response of dendritic cells, which have protective effects on the development of mucosal immunity. These HMO-related mechanisms may work together to prevent allergic diseases in breastfed infants [48]. In various studies performed in human infants, HMOs also showed positive protective effects against infections, such as those caused by *Campylobacter*. However, there is a lack of studies on infant health [49].

Additionally, a link between human milk and allergic outcome in later life has been published in 1936 by Grulee and Sanford [50]. A number of studies have reported this association [51-56].

Newborns may develop allergic diseases because their immune system is dominated by T helper 2 cell (T_H2) responsiveness during the neonatal period [57]. Shifting the immune response towards a more T helper 1 (T_H1) of the prone and regulatory type favors the development of immune protection and balanced immunologic responses [58]. Epithelial barrier and mucosal homeostasis are important in the prevention of allergic sensitization and have evoked interest. HMOs could support this function by enhancing proper epithelial maturation and helping to compose microbial colonization [59-61].

MICRO RNAS IN HUMAN MILK

Micro RNAs (miRNAs) modulate the activity of specific mRNA targets and are known to play important roles in both physiological and pathological processes in mammals. They are also involved in immunologic reactions [62]. Serum miRNAs can be used as potential biomarkers for various cancers and other diseases. miRNAs in human milk were first profiled in 2010 by Kosaka et al. [63], who also reported high expression levels of immune-related miRNAs in the first six months of lactation. Until this study was reported, the physiological roles of body fluid miRNAs were undetermined.

Almost 1,400 different mature miRNAs have been documented in human breast milk, which vary in colostrum, mature milk, milk cells, milk lipids, and milk exosomes [64]. After being transported to the intestine through lactation, miRNAs remain intact in the degradative processes of digestion and are absorbed by epithelial cells. Then, miRNAs reach various tissues and organs, where they perform immunological functions and developmental programming in the infant immune system [65].

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STEM CELLS IN HUMAN MILK

The presence of stem cells in the mammary gland was first postulated because the mammary epithelia expand and regress throughout adult life [66]. Mammary stem cells (MaSCs) are present in a quiescent state and in few numbers in the resting breast, but become activated during pregnancy and lactation, as if programmed for proliferation, differentiation, and apoptosis [67]. During the development of invasive breast carcinoma, MaSCs implicate both mesodermal and endodermal organs [68,69]. This indicates that the mammary gland harbor stem cells with self-renewal capabilities, both in normal and aberrant conditions. The molecular determinants and regulators of MaSCs are poorly understood. Human lactating breast tissues contain a greater number of activated MaSCs [70]. Hassiotou et al. [71], reported that human milk contains stem cells (human breast stem cells, hBSCs) that contain many genes present in human embryonic stem cells (hESCs), which contain factors for core self-renewal circuitry of hESCs. They also reported that hBSCs differentiated into cell lineages from all three germ layers in vitro, suggesting the potential of hBSCs for use in research on adult stem cell plasticity and breast cancer.

EFFECTS OF PASTEURIZATION AND STORAGE ON THE COMPONENTS OF HUMAN MILK

Most mothers store their expressed milk in a refrigerator or freezer for long periods, during which the immunological components, micronutrients, and diverse trophic factors as well as the dynamic nature of the milk composition may be altered. These changes were also noted in pasteurized cow and human milk, in which the levels of sIgA, lysozyme, cytokines, TGF-β, lipases, and adiponectin were reduced [72,73]. Specifically, the levels of IFNγ, TNFα, IL-1β, IL-10, and hepatocyte growth factor were found to be significantly reduced following Holder pasteurization (62.5°C for 30 minutes) of donated human breast milk [73]. Freeze–thaw cycles also cause some damage to the lysozyme, IgA, and lactoferrin components, as was frequently noted in some donor milk for preterm babies [74].

CONCLUSION

The ingredients in human milk that contribute to its immunomodulatory effects are extremely diverse, and each bear characteristics that need to be individually studied. Such knowledge can help sufficiently educate breastfeeding mothers and thus ensure good health of their babies.

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