

The influence of natural feeding on human health: short- and long-term perspectives

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Abstract

Breastfeeding is the most appropriate way to nourish infants. It promotes proper physical and intellectual development of the child. Human milk is unique and impossible to replicate with any other kind of food. However, using maternal milk not only has beneficial effects on the infant's health but it can also help to prevent illnesses in adulthood. Breastfeeding improves immunity and consequently decreases the occurrence of infections, especially those of the gastrointestinal tract and respiratory tract. Moreover, it helps to reduce the risk of some disorders such as allergies, diabetes mellitus type 1, obesity and arterial hypertension.

Introduction

The diversity and complexity of the functions of the bioactive ingredients present in colostrum and mature human milk feeding extend far beyond simple, natural child nutrition. Modern technologies, molecular medicine, clinical diagnostics and therapy have allowed discovery of more and more information about the specific properties of natural food, the mechanisms of action of individual components and their significance for human health. It should be emphasized that the beneficial effects of biologically active compounds apply to a number of positive and negative genetic and environmental factors determining the functioning of the body. This makes it difficult to directly evaluate the impact of the various components of human milk, especially in the context of long-term studies and chronic diseases.

Currently, a World Health Organization (WHO) resolution recommends feeding only with breast milk for the first 6 months of life and extends it, at least until the child's first year of life, after the introduction of complementary foods. The start and end times of breastfeeding are fundamental to further health [1]. Each of the organs or systems of the human body are characterized by a so-called critical period – a time of intensive development. In this period the action of harmful factors,

inter alia longer-lasting quality-malnutrition, can lead to irreversible morphological and functional damages. Mother's milk (in the case of healthy women) is a type of liquid tissue, which is the most suitable food for the child. It consists of components suitable for building immature gastrointestinal mucosa, the central nervous system, endocrine system and immune system, and determines the proper development of other systems. Human milk contains essential vitamins, minerals and other important components, such as nucleotides and DNA, which are not present in any artificial milk [2, 3]. It should be noted that the composition of breast milk is not constant and depends on the nutritional status of the mother, her diet, period and phase of lactation, and time of day. Human milk is species-specific, has an appropriate caloric value, contains essential nutrients and adjusts its composition to the developmental needs of the infant [4].

The aim of present paper is to review and systematize the literature in the field of active ingredients in human milk, with particular emphasis on factors affecting immunomodulation and the human metabolism. Most studies relating to this topic focus on the benefits of the short-term supply of nutrients in human milk, but there are few studies on the effect of long-term

health. Recent studies show that the active ingredients in breast milk play a much greater role than is generally supposed, going far beyond the provision of nutritional products for the breast-fed baby. Therefore, the present paper analyses the impact of the length of breast feeding on the incidence of gastrointestinal inflammation and respiratory diseases, allergies, diabetes and hypertension in childhood and in later life. The spread of information about the positive effects of long-term breast-feeding and the mechanisms of action of the active ingredients of breast milk may still change too small the percentage of naturally nourished newborns and infants in Poland.

Active ingredients in human milk

The presence of a variety of active substances in the fluid produced by a woman's mammary glands makes for a natural food that is impossible to artificially copy. Breast milk contains several enzymes that facilitate the proper digestion of nutrients in the baby's body. An appropriate protein to fat ratio (1 : 3) and the correct proportion of casein to whey proteins (3 : 1) to increase the bioavailability of natural food, make human milk a good source of building, functional and energetic components. Of particular importance are the long-chain polyunsaturated fatty acids, for example arachidonic acid and docosahexaenoic acid (for development of the brain and retina) and cholesterol (a component of cell membranes and a precursor of bile acids and vitamin D). Among the carbohydrates essential for the development of the child, the most frequently referred to are lactose (as the main source of sugar and energy) and galactose (a component of galactolipids, which play an important role in the proper development of the central nervous system). Other important components of this natural food are medium-chain triglycerides, which increase the absorption of other products by slowing intestinal motility [1].

Among the best-known human milk components are lactoferrin, casein and α -lactalbumin, which are characterized by their multi-action [2, 5–7]. Lactoferrin is active against Gram-negative and Gram-positive bacteria, enveloped and non-enveloped viruses, and some types of fungi and parasites. It has also immunoregulatory, antioxidant and anticancer properties [5, 8, 9]. Lactoferrin stimulates growth and protects the epithelium of the intestine, increases the absorption of iron and participates in the regulation of haemopoiesis. It should be noted that it exhibits a high resistance to the proteolytic action of gastrointestinal digestive enzymes [5]. In animal studies, lactoferrin given orally, or intravenously in the case of endotoxemia, protects the intestinal epithelial layer, particularly its consistency

within the villi. In addition, it stimulates the production of protective mucus, reducing bacterial translocation and the development of sepsis. It was found that after oral administration of lactoferrin, the production and release of cytokines and other factors involved in the inflammatory response were changed (such as interleukin 1 and 8 (IL-1 and IL-8), tumor necrosis factor- α (TNF- α), histamine and reactive oxygen species). Lactoferrin also stimulates anti-inflammatory agents (such as IL-10, IL-4 and IL-6). Additionally, it activates the reticuloendothelial system (connective with monocyte and macrophage) and affects the function of neutrophils [5].

Milk casein showed a protective effect in the experimental bacteraemia and endotoxemia associated with the oral administration of *Escherichia coli* and the lipopolysaccharide isolated from *Salmonella typhimurium*. It was associated with higher levels of IgA in the blood, intestines and faeces, and increased IL-5 and IL-6 production by murine splenocytes [10]. Casein hydrolyzate is used in groups of infants with a high risk of developing diabetes type 1, showing a decreased risk of disease over the following 10 years in comparison with the standard milk formula [7]. Probably this was related to the promotion of pancreatic islet neogenesis without affecting the activity of T cells [7, 11]. In addition, the peptides (resulting from casein hydrolysis) showed a hypotensive effect. *In vitro*, milk casein decreased levels of angiotensin II by inhibiting the enzyme responsible for the transformation of angiotensin I. A diet based on casein hydrolysate alleviated infant colic symptoms associated with food allergies [12]. This was connected with the analgesic and sedative properties of peptides resulting from hydrolysis of the protein. Use of α and β milk casein and their trypsin degradation products has an effect on the metabolism of calcium and phosphorus, and demineralization of enamel in people. In addition, it limits the development of caries in patients with dry mouth syndrome [13]. It is worth noting that anti-tumour activity has been demonstrated for casein (when orally administered in experimental animal models) [11].

α -Lactalbumin (LA) demonstrates anti-inflammatory, antiviral, antidepressant and anti-tumour properties. A diet rich in protein prevented diarrhoea after experimental bacteraemia (with enteropathogenic strains of *Escherichia coli*) in rhesus monkeys. Its effect has been demonstrated for the transport of water and sodium ions through the wall of the gastrointestinal tract. Orally administered LA led to faster weight gain in malnourished children and improved water management in comparison with conventional foods (without affecting people with normal weight). *In vitro* α -lactalbumin demonstrated activity against HIV-1, probably connected with inhibition of viral protease and integrase [11].

Moreover, this protein, rich in tryptophan, increased production of serotonin (SER) and SER availability in the brain. Additionally, LA decreased cortisol secretion, and thus the frequency and severity of depression and anxiety in animals with high stress [14]. It also showed an antiulcer action and protective properties in relation to the gastric mucosa, connected with prostaglandins (particularly PGE₂), which stimulates the secretion of mucins and inhibits overproduction of hydrochloric acid (normalization of gastric pH). The products of enzymatic digestion of proteins – α -lactorphine – by acting on the endothelium, supported the relaxation of blood vessels induced by acetylcholine in rats with a tendency towards spontaneous hypertension. This was associated with increased activity of nitric oxide synthase. In the absence of a tendency towards blood pressure disorders, α -lactorphine did not show this action. Another hydrolysis product of α -lactalbamin, the peptide lak-tokinin, in an *in vitro* study, inhibited the angiotensin

l-converting enzyme and reduced release of endothelin 1 by about 30%, which enlarged the lumen of blood vessels. The above-described peptides were involved in the regulation of blood pressure without affecting heart rate [15]. It is worth adding that while the LA antitumor mechanism of action is poorly understood, it is known that α -lactalbamin inhibited tumour growth by inducing apoptosis of neoplastic cells [11]. In the case of mice that were genetically predisposed to breast cancer, the use of vaccines based on LA prevented the formation of malignancies [16].

Shortly after birth, babies do not yet have defence mechanisms, so substances supplied with food that possess immunomodulatory properties are particularly important. Human colostrum and milk also contain macrophages, B and T lymphocytes, granulocytes, epithelial cells of the mammary glands and mesenchymal stem cells [17]. The number of these cellular components is not uniform and depends on the lactation pe-

Table I. Some specific and non-specific immunological components of human milk

Active component	Functions
Secretory immunoglobulin A	Covers gastrointestinal mucosa with a tight layer preventing the penetration of pathogenic microorganisms and allergens
Haptocorrin	Cobalamin binding, which is essential for the growth of bacteria
Oligosaccharides	Stimulates the growth of bacteria of the genus <i>Lactobacillus</i> and <i>Bifidobacterium</i>
Fatty acids	The damage of lipoprotein caps of some viruses
Glycoprotein 90K	Neutralizes particles of respiratory syncytial virus, reducing the incidence of respiratory infection
Interferon- γ	Modulates the activity of immune cells
Epidermal growth factor	Accelerates the maturation and regeneration of epithelial cells
Lactoferrin	Binds iron, so that element becomes unavailable for bacteria, which inhibits their growth; anti-inflammatory, antioxidant and anti-tumour properties
Lysozyme	Bacteriostatic effect by damaging the cell walls of pathogenic bacteria
Mucilages	Prevents the adhesion of bacteria onto the gastrointestinal wall
Cytokines (TGF- β , interleukin IL-1 β , IL-4, IL-8, IL-10)	Omni-regulatory action on immune processes
B cells	Takes part in the production of antibodies
Fibronectin	Stimulates the activity of macrophages
Th cells	Takes part in the production of cytokines, including interferon- γ
Tc cells	Destroys cells that cannot properly fulfil their function as a result of infection by viruses and mutations
Macrophages	Their main task is the phagocytosis and the production of lysozyme and cytokines
Neutrophils	Bacteriostatic and phagocytic properties

TGF- β – transforming growth factor- β . Source: own modifications based on: [5, 17, 19–23]

riod, the state of the mother's and child's health, and genetic predisposition. For example, in the human milk from mothers of children with respiratory tract infections, the total number of immune cells is higher than in the milk from mothers of healthy infants [18]. Macrophages contained in the human milk release cytokines and many other immune factors including lysozyme, lactoferrin, IL-1, IL-6, IL-8, TNF- α and granulocyte-macrophage-colony-stimulating factor (GM-SF). Detailed immunological properties of selected components of human milk are shown in Table I [17, 19–24]. It is worth noting that, besides active substances mentioned in the above statement, human milk also contains leptin, fibronectin, melatonin, erythropoietin, polyamines, nucleotides and DNA [2, 3]. The presence of these ingredients in the diet helps children in the transition from an intrauterine safe environment to the outside world.

Operating range of immunomodulation

The direct impact of breastfeeding is revealed by a decrease in the number of infections (especially of the respiratory and digestive systems) as well as a shorter duration of systemic infections. The supply of human milk accelerates the maturation of the respiratory system. Breastfeeding also affects the functioning and integrity of the gastrointestinal tract and creates an appropriate bacteriological barrier. Diet, especially in the first period of life, can program the systemic metabolism by affecting the activity of enzymes as well as immune and endocrine functions.

Feeding a child generates the appropriate immune memory for the body. The balance between the mechanisms of tolerance and active immune response governs the protection system against infections, allergies and autoimmune diseases [20]. A lack of stability and poor formation of the immune response to antigens during infancy and early childhood, promotes the occurrence of chronic diseases later in life.

An overview of 20 independent clinical studies showed that infants exclusively breastfed during the first 6 months have lower morbidity associated with acute and chronic gastrointestinal infections, compared with children nourished with mixed food from 3–4 months of age. Breastfeeding and the time of the first administration of human milk significantly reduce the incidence of rotavirus infection. Moreover, the supply of this milk showed an improvement in the clinical course of these infections. Studies have shown that the peak incidence of the above-mentioned diseases among breast-fed infants takes place in the sixth month of life, and among artificially fed infants, in the first month [8, 20, 25, 26].

In the case of adenovirus infections in children and adults, the protective role of breastfeeding has been demonstrated. The symptoms of these infections are primarily of the gastrointestinal tract (diarrhoea), and respiratory system (rhinitis, pharyngitis, otitis media and pneumonia) [8, 27]. It was found that the use of probiotics containing *Bifidobacterium lactis* and *Lactobacillus rhamnosus* as dietary supplements by breastfeeding women increased the concentration of tumor growth factor- β (TGF- β) and IgA in secreted milk [19, 22]. Of 12 independent clinical studies 8 showed a positive effect from high concentrations of TGF- β 1 and β 2, such as use of a natural diet to lower the incidence of atopic dermatitis. Supplementation of the probiotics mentioned above also functions as an antiallergic strategy [23]. The long-term effects of giving breast milk, depending on immunomodulation, are reduced inflammation and autoimmunity reduced autoimmunity, as well as improved resistance against pathogens [25, 26].

The effects of infant feeding on allergies, type 1 diabetes, obesity and hypertension

The families of people affected by allergies, according to the guidelines on the primary prevention of allergic diseases, are recommended to continue breastfeeding for at least the first 6 full months of life [19, 28, 29]. This is particularly important because epidemiological studies have shown that the incidence of allergic diseases has increased exponentially in recent years, especially among children. Allergies with symptoms in the upper respiratory tract include more than 30% of the population in some countries (UK – 37%, USA – 34%). Alarming data on skin allergies show that they occur in approximately 20% of people [30, 31]. The most common allergic diseases include rhinitis, asthma, extrinsic alveolitis, urticaria, atopic and contact dermatitis, swelling of vasomotor, allergic and migraine headaches, sinusitis and conjunctivitis, and food allergies. The latter are particularly true of infants and young children [32]. The mechanism of the protective effect of human milk components against allergic diseases is known only to a small extent. Probably less allergenicity of administered food plays an essential role in these mechanisms. Moreover important are: the possibility of strengthening the intestinal mucosal barrier and the tolerance induction involving complex immune responses [33, 34].

Breastfeeding has some protective effect against the development of type 1 diabetes [6, 7, 26, 33]. A meta-analysis of 17 independent studies showed that this disease is more common in people fed from early infancy with mixtures based on cow's milk. The differences were statistically significant at 19–27%,

and showed a higher incidence of cell antibodies (anti-insulin, against tyrosine phosphatase or glutamic acid decarboxylase) in the absence or the short use of breastfeeding (less than 12 weeks) [26]. This is probably associated with the presence in human milk of numerous cytokines, immunoglobulin A and growth factors such as insulin-like growth factor 1 (IGF-1), which affect the maturation of the child's lymphoid tissue. It was demonstrated that natural casein derived from food has a positive effect on the proliferation of Langerhans cells, which produce insulin. As mentioned above, protein hydrolysates administered to infants at high risk of developing type 1 diabetes significantly reduced the incidence of this disease (long-term observations), in comparison with conventional artificially nourished milk formula [7]. In addition, it is important for the presence of insulin in human milk, which is a protective factor against the development of glucose intolerance. It should be noted that the damage of islet β cells (with subsequent insulin deficiency) in type 1 diabetes is probably caused by use of animal milk (which includes gluten and/or lactoglobulin). Patients diagnosed with the disorder had elevated levels of antibodies against β -lactoglobulin, characteristic of the blends of nutritional products based on cow's milk [35].

Meta-analyses taking into account the body mass index (BMI) of parents, their level of education and the presence of tobacco consumption in the mother, including more than 300,000 people, have shown that artificial feeding in infancy is an independent risk factor of obesity in childhood and adulthood [36]. The protective effect of breastfeeding against significant overweight in children and adolescents has also been shown in population studies in the Czech Republic and Germany, including respectively 33,000 and 10,000 people. These analyses *inter alia* demonstrated the relationship between the length of feeding during the first year of life and the prevalence of overweight and obesity in the age range 5–6, and at 14 years old. It has been estimated that natural feeding reduces the risk of obesity in young people by 20% [8, 33]. It is believed that it limits the exposure of the infant to high-protein and high-milk substitutes [25]. The content of protein in food materials is about 1.6 times higher than it is in human milk. This implies a greater discharge of growth hormone, insulin-like growth factor 1 and insulin into the bloodstream, resulting in adipocytes and of stocks of fat in artificially fed infants compared with naturally nourished individuals [33, 37]. Furthermore, it is suggested that as well as substitute feeding mixtures, a significant risk factor for obesity in children is posed by excessive maternal nutritional status during pregnancy, which has an impact on the development of the foetus [36, 37].

Breastfeeding also plays a beneficial role in the regulation of blood pressure in adulthood. It has been shown that it is lower in those fed naturally in childhood, as compared to formula fed children [25]. Initially there is little difference, but in adulthood this disparity may have important clinical significance. Based on meta-analysis, it has been estimated that a reduction of blood pressure by an average of 2 mm Hg is associated with a 17% lower tendency towards hypertension in the future and a reduction in the number of cases of heart attack and stroke between 6% and 15% [38]. It is believed that the mechanism is mainly related to the presence of casein hydrolysis products that have antihypertensive properties (lowering blood levels of angiotensin II) and a relatively low sodium content in the natural diet. Cow's milk, compared to a human's milk, has three times more of this component. It should be noted that until the 1980s, nutritional compounds used in neonates and infants were characterized by high levels of sodium. Currently, artificial milk (powder) in this respect is closer to human milk, but this also depends on the type of water used in the preparation of the artificial milk. Often parents are not aware of the need of use low sodium fluids in the preparation of food. It should be noted that the impact of breastfeeding on the normalization of blood pressure is small, but it remains important because of the overlap between the different effects of feeding. As already mentioned, this results cause the reduction of overweight and obesity, which further reduces the incidence of hypertension during development and adulthood [25].

It is worth noting that there have been many studies concerning the impact of natural feeding on the risk of developing diseases during adulthood; however, they are not always clear on the role of nutrition during infancy. For example, in atherosclerosis, Crohn's disease and rheumatoid arthritis most of the data points to the positive effect of breastfeeding, lowering the incidence of these diseases. These tests usually include a few research groups, or they were not randomized, which reduces their importance [9, 25, 26].

Summary

The present analysis showed the uniqueness of natural milk resulting from its wealth of qualitative and quantitative components and the impossibility to fully replicate its composition in an artificial way. It is the optimum source of nutrients required for construction and proper development of the immature gastrointestinal tract, central nervous system and endocrine and immune systems, which determine the proper functioning of the whole body. The beneficial effects of such food components do not end with the cessation of breast-

feeding. Improved health and reduced risk of diseases, especially of the digestive, respiratory and immune systems, can be seen in adulthood. Children breastfed for a long duration rarely suffer in the future from lifestyle diseases such as obesity, type 1 diabetes or hypertension. The mechanism of action of active ingredients in human milk is known only to a small extent. The data that we have found indicate, however, that feeding children with breast milk for at least the first few months of life is the best investment in their physical health and normal intellectual development. The use of artificial mixtures should be reserved only for cases where breastfeeding is not possible.

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